

A RESEARCH INTO THE PHYSIOLOGY
OF THE PULMONARY CIRCULATION.

by

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Please turn the pages with care.

GENERAL ARRANGEMENT.

1. HISTORICAL INTRODUCTION.
2. THE ACTION OF PITUITARY EXTRACTS ON THE PULMONARY CIRCULATION.
 - (a) Experiments on vessels of surviving lung.
 - (b) Experiments on living animals.
 - (c) Summary.
 - (d) Observations on the research.
3. ON SPONTANEOUS MOVEMENTS IN BLOOD VESSELS WITH SPECIAL REFERENCE TO THE PULMONARY CIRCULATION.

This thesis is accompanied by 49 original kymographic records, each of which is self-explanatory in addition to the description given in the text.

P A R T I.

HISTORICAL INTRODUCTION.

Although the existence of the pulmonary circulation plays such an important part in the history of the discovery of the circulation, our knowledge of the physiology of the lesser circulation is still comparatively scanty and many reputable text-books give it but a passing reference.

Even Galen (125-201) had an idea, however rudimentary, of the pulmonary circulation. He assumed however that the blood of the arteria venosa (pulmonary vein) flowed back from the lungs at each systole, by a sort of physiological insufficiency of the mitral valve in order to expel by expiration the pulmonous vapours formed in the blood. He thus allotted to the pulmonary vein a double and opposite function, namely that of carrying the arterial blood from the lungs to the heart and then returning a portion of it with the vapours from the heart. The errors of this systolic reflux and the porosity of the septum have weakened greatly the lustre of Galen's name in connection with the pulmonary/

pulmonary circulation, but even Harvey himself recognised that Galen was the first to have any idea of it, more particularly in a passage in "De usu partium".

The first to rectify and complete the Galenic doctrine by denying the permeability of the cardiac septum and affirming the passage of the blood from the right to the left ventricle through the lungs was Servetus, a Spanish theologian and physician in the year 1553. For the publication of his notable book, "Christianissmi re²stitut¹or", he was burnt at the stake in Geneva in the same year at the investigation of Calvin because he would not recant his faith, part of which was briefly that a knowledge of the spirit of God demanded a knowledge of the spirit of man, and a true knowledge of the spirit of man necessitated a knowledge of the structure and working of the body in which that spirit resides. In all fairness it should however be added that his earlier book "De Trinitatis Erroribus" in which he stands as the pioneer of Unitarianism contributed very largely to his downfall. In 1559, a Cremonese anatomist, Columbus, prosector to and later successor to Vesalius in Padua claimed priority for the discovery of the pulmonary circulation, and historical records contain/

contain much interesting argument on the subject. Such eminent scientists as Willis and Foster support Servetus, while Ceradini (1876-77) and Roth, whom Tigerstedt calls the most learned anatomist of the sixteenth century, attribute the discovery to Columbus. The arguments together with the somewhat difficult attitude of the great anatomist Vesalius who has done so much towards the refutation of so many of Galen's original theories in other parts of the circulation, are too lengthy to be entered into here, apart from the fact that there seems little doubt that Vesalius, as seen from his early writings, learned the impermeability of the septum from his prosector Columbus at Padua as early as 1542, although there is no mention of its physiological corollary, the pulmonary circulation.

With the work of Cesalpinus, Sarpi, De Vinci and its subsequent consummation by Harvey, the general relation of the pulmonary to the systemic circulation becomes clear.

Since the time of Harvey, much advance has been made in our accurate knowledge of the systemic circulation, but our knowledge of the pulmonary circulation has not advanced nearly so rapidly, while the accurate relationship between the two circulations is/

is only now becoming known.

The main hindrance has been the great experimental difficulty in connection with work on the pulmonary circulation, that the chest has to be opened, and branches of the pulmonary artery are difficult of access; while most of the earlier investigators did not realise that the pulmonary blood pressure was much lower than the systemic.

The first observations on the pulmonary circulation were made by Ludwig and Beutner in 1850. They opened the thorax under artificial respiration and introduced a cannula into the left pulmonary artery. The values elaborated by Beutner (1882) have not been materially altered even by the most recent observations.

Chaveau and Faivre avoided opening the thorax and passed a trocar and cannula connected with a manometer directly into the pulmonary artery of a horse through an intercostal space, but the use of such a method is obviously limited. The later investigations of Bradford and Dean in 1888 are more important. These workers, using dogs, resected two or three ribs in the back and inserted a cannula into the artery of the lower lobe of the left lung, the animals being under the influence of morphia and/

and on artificial respiration.

Since that time, several observers have studied the pulmonary circulation and the majority have inserted a cannula into one of the branches of the pulmonary artery after opening the thorax in front. The majority also have used a mercury manometer which does not show the smaller variations seen in the pulmonary circulation. There have however been one or two exceptions. Mellin, who worked extensively on the action of drugs on the pulmonary circulation, used a special variety of cannula which he inserted through a slit in the wall of the pulmonary artery, but unfortunately he too used a mercury manometer. François Frank first substituted a water (anti-coagulant solution) manometer or it may be said returned to the original water manometer of Vierordt but he connected it to a Marey's tambour and used a plethysmographic method.

The Starling heart-lung preparation, and an electrical method (Edmunds & Desbouis & Langlois) have also been used.

Moreover the effect of respiration on the pulmonary pressure was apparently neglected by early observers, the chest being left open and artificial respiration used. Knoll (1888) who introduced
a/

a cannula into the main pulmonary artery was the first to close the chest and allow the animal to breathe naturally, but as he used a mercurial manometer he did not achieve much. Wiggers, by whom much recent work has been done, resected pieces of the 7th and 8th ribs of the right side of dogs and introduced a cannula into a small accessory branch of a lobar artery connecting it by an air-tight system to a special tambour, from the movements of which the pressure could be calculated. For the majority of his work, however, he was satisfied with pressures recorded in the right ventricle and with making deductions regarding the pulmonary circulation.

The results of these various methods have been so different that the pulmonary circulation has been somewhat avoided.

In 1919 however Sharpey Schafer introduced a new and very convenient method of recording the pulmonary blood pressure and as a result a new era of investigation of the lesser circulation may be considered to have been entered upon. Its use has already thrown considerable light on the subject. This method has been used in the present research and further reference is made to it below.

In/

In addition to experiments made directly upon the blood pressure, some study has been made of excised rings of the pulmonary artery.

Investigation has also been made by perfusing the vessels of the surviving lung. In this connection the work of Brodie & Dixon is of special importance. These observers elaborated a method for perfusion of the systemic circulation and proceeded to apply it to the pulmonary without any apparent regard to the differences in pressure which normally exists between these two circulations. With the high pressure (30 mm. Hg.) oedema rapidly set in with Locke solution and they found it necessary to use defibrinated blood. By doing so they introduced another disadvantageous factor, namely, that the fluid used for perfusion was of greater viscosity than the fluids with which it is generally convenient to dissolve the substance to be tested. The majority of the results obtained by them on the pulmonary circulation - notably that of adrenalin - have not been confirmed, but owing to the otherwise high standing of these investigators a considerable amount of confusion has been caused. More recent workers have found Locke solution quite satisfactory, and in this research the method elaborated by Sharpey Schafer and Lim has been used, the general principles of which are given below.

P A R T 2.THE ACTION OF EXTRACTS OF THE POSTERIOR LOBE OF THE
PITUITARY BODY UPON THE PULMONARY CIRCULATION.

A thorough research into the action of pituitary extracts has not yet been undertaken, presumably largely because of the experimental difficulty and the diversity of results in the investigation of simple substances, the nature of whose action is better understood. A few observations, however, have been made.

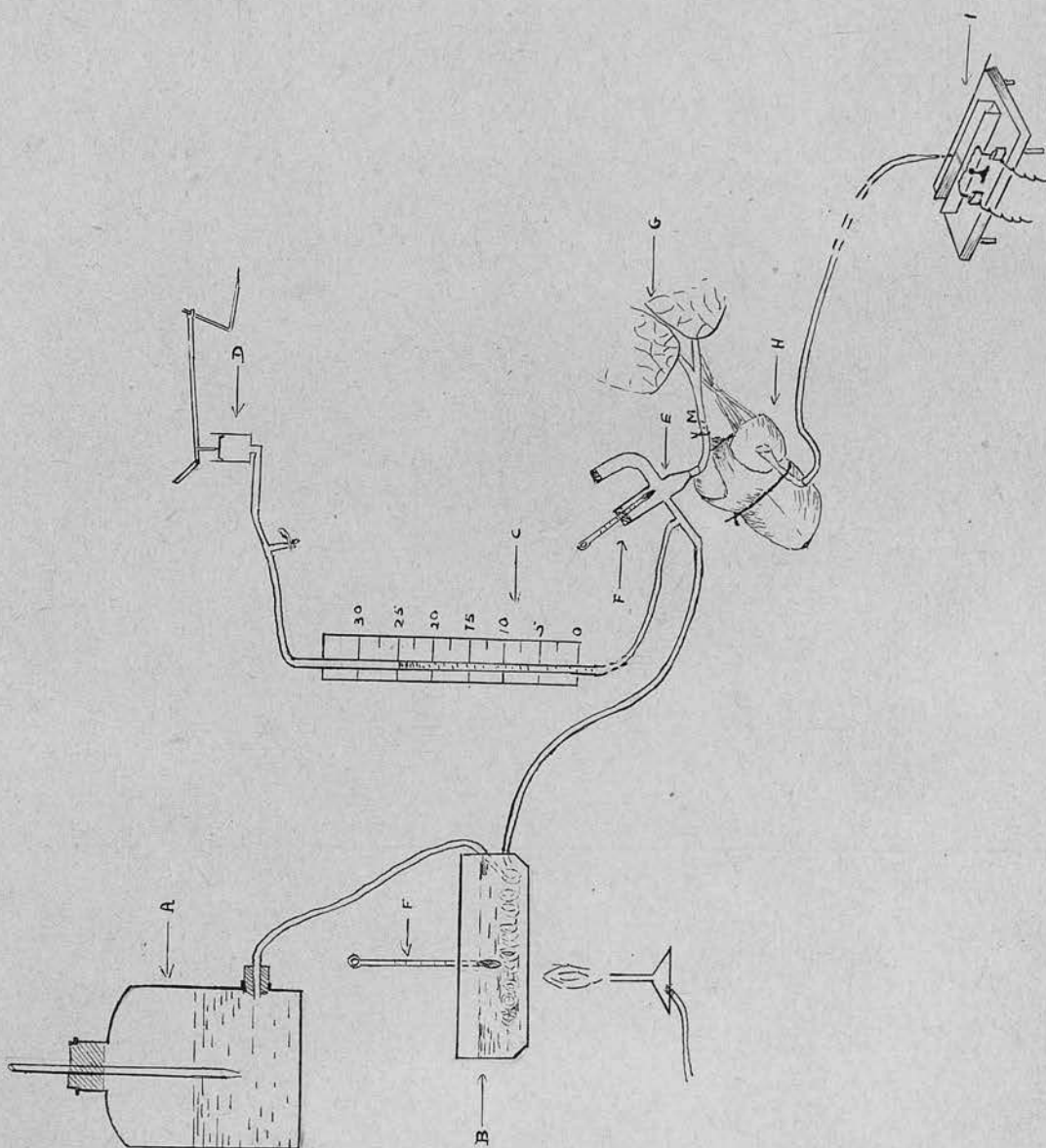
Cow was unable to obtain any action of such extracts upon isolated rings of the pulmonary artery, although the action on other arteries except the coronary was most marked. De Bouis and Suzanna however obtained a marked constriction which persisted for several hours and this was confirmed by Dale who also made "a few" perfusion experiments with similar results. Argyle Campbell working in this laboratory obtained constriction or dilatation according to the nature of the fluids with which the extracts were made. In perfusion experiments, however, he obtained constriction only, but with a carefully neutralised solution.

In the experiments described below the commercial pituitrins of Parke Davies & Co. and of Martindale were used, and also pituitary extracts made by myself. Fresh ox pituitaries were obtained from Willows, Francis, Butler and Thomson. The posterior lobe with the pars intermedia was dissected out, sliced and dried on a glass plate in an incubator at 37°C. The pituitaries were then powdered and kept dry till required. Solutions were made up fresh by boiling a weighed amount of the powder with Ringer-Locke Solution (with or without bicarbonate) for ten minutes, after which the protein was filtered off. The solutions, unless otherwise stated, had a strength of $2\frac{1}{2}\%$.

The experiments divided themselves into two series, the action of the pituitary extracts on the surviving vessels of the lung and the action on living animals.

Action on the surviving vessels of the lung.

The animals used were cats and rabbits at least half grown and varying in size. They were anaesthetised with chloroform and tracheotomy carried out. They were then placed on artificial respiration with heated air, the internal mammary arteries prevented from bleeding in the usual way by passing a ligature round the sternum in the 2nd interspace, and the chest opened by reflecting the muscles and cutting through three or four ribs near their attachment to the sternum. The sides of the opening were drawn apart with hooks, blunt dissection made down to the pericardium which was opened and the heart exposed. Artificial respiration was reduced to the minimum capable of sustaining full action of the heart, thus precluding any undue pressure on the lung capillaries and the ligatures placed in position. One ligature was passed round the pulmonary artery, including the aorta, and the other round the base of the ventricles. The anaesthetic was then removed and at the first evidence of recovery the animals were bled to death by severing the carotid arteries. This latter procedure avoided much haemorrhage and the/



References

- A—Marriott's Bottle.
- B—Heater & spiral.
- C—Water Manometer.
- D—Ellis Piston Recorder.
- E—Cannula $\frac{1}{2}$ inch catch air bubbles.
- F—Thermometer.
- G—Lung.
- H—Heart & cannula tied into left auricle.
- I—Schaker's filter.
- M—Cannula tied into Pulmonary artery.

From this cannula the fluid was led by a short rubber tube to the inlet perfusion cannula which was so curved as to avoid kinking, and a minimum of disturbance of the natural alignment. From the outlet cannula the fluid was led to a mechanical tilter, each tilt of which was registered on the kymograph by an electric signal. The water (perfusion fluid) manometer was connected by an air-tight system to an Ellis piston recorder, a continuous record thus being obtained of the actual pressures used, further any constriction of the blood vessels causing an obstruction to the flow through the pulmonary circulation caused a rise in the pressure shown, and similarly a dilatation was shown by a fall.

The pressure was so adjusted that there was a free continuous flow from the outlet tube. The perfusion fluid used was Ringer-Locke Solution at $37^{\circ}\text{C}.$, although a considerably less temperature - even $20^{\circ}\text{C}.$ - did not appear to make any difference to the results. The Ringer-Locke Solution was made up with and without sodium bicarbonate solution and had the following composition.

| | | |
|------------------|----------|----------------------------|
| NaCl. | $.92\%$ | <i>in distilled water.</i> |
| KCl. | $.04\%$ | |
| CaCl_2 | $.02\%$ | |
| NaHCO_3 | $.075\%$ | |

Brodie and Dixon have, as already indicated, stated that the use of such a fluid is quite inadmissable owing to the rapid onset of oedema. With careful adjustment of the pressure to the minimum necessary, oedema however did not occur usually for two hours or longer after the commencement of the perfusion and in a small degree it did not appear to alter the results obtained. The use of pituitary extracts which it will be seen below have usually some dilator effect on the pulmonary blood, no doubt contributed to the delay of the onset of oedema, by preventing the necessity of the use of high pressures.

The additions of the drug to be tested was simply made by injecting them with a syringe through the rubber tubing just before the 5-way cannula. At first sight, this seems disadvantageous as there is a rapid but temporary rise in the manometer level. This might be considered to cause a constriction of the arteries as a result of the sudden dilatation which has been shown by Poiseuille^u and by Bayliss to have such an action. Controls, however, have been taken and it has been clearly seen that if a fluid of the same/

same nature and temperature be injected there is no arterial response. This point is further referred to below. It was also noted that considerable variation of the temperature of the injection fluid made no difference to the results obtained. When, however, experiments were carried out at night and solutions standing in the laboratory were very cold, a contraction could be obtained with Ringer-Locke fluid at these low temperatures. In carrying out experiments therefore, this factor was eliminated by raising to body heat all fluids prior to injection.

Unless otherwise stated it is to be presumed that the results were obtained both with the commercial pituitrin (P.D. & Co.) and extracts made by the writer.

The accompanying tracings give examples of the results of these investigations. A few animals, notably those in poor condition and whose tissues were dry, did not respond to extracts.

Generally the result of the first dose was a marked constriction only, which took a long time to pass off or was persistent (Fig.2.)

For reasons given below the initial sharp rise and fall due to the mechanical action of the injection can be neglected.

With/

19

140

303. 7.1 M
100 1013

290

220

315

Cat, female
2500
16-11-20

1cc. Pituitrin. (Machindale) 1st Dose.

Injection just before
feeder.

Note Marked constriction shown by rise in manometer and
diminution of outflow as shown by filler - each 1/11 = 4.5 cc.

The second & subsequent doses gave a rise and fall.
This melhoo was given up for reasons given in the let.

Pressure of

Tilber

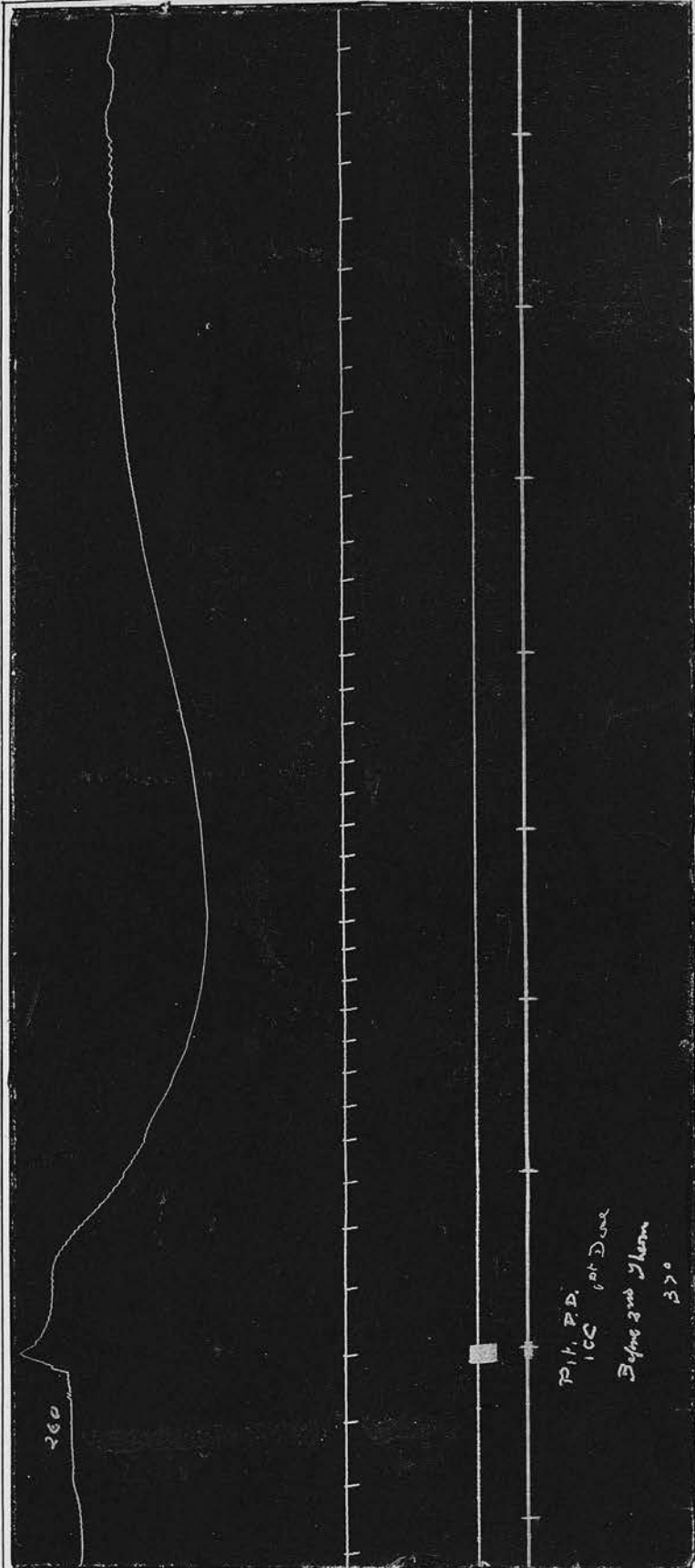
Signal.

Time

Rabbit, female

100-2000

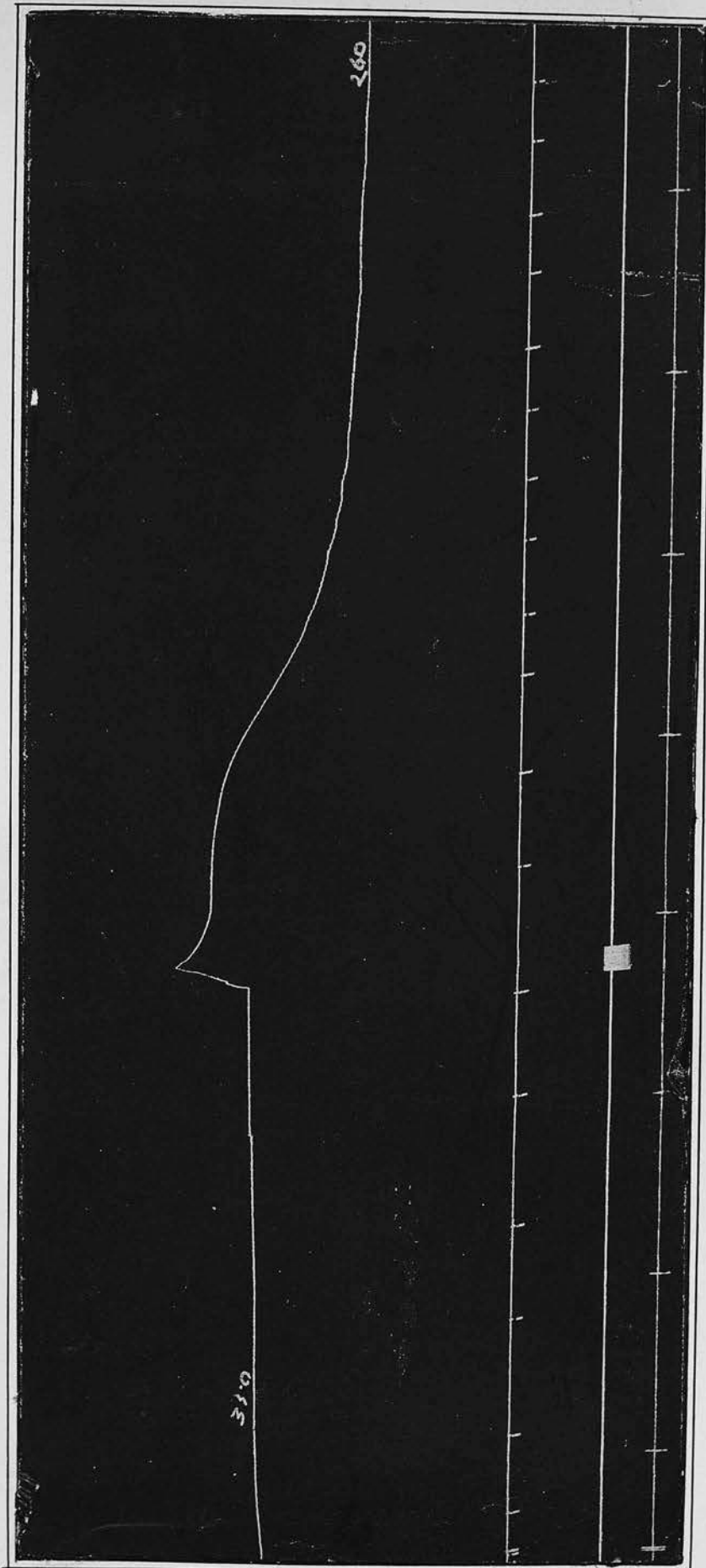
26-11-20.



1 cc. Pituitrin (P.D.) 1st Dose.

№ 6/2

Rise and fall in manometer indicating constriction then dilatation of pulmonary vessels. Change in rate from outlet tube well shown by faller - each fall = 4.5 cc.



100. Pituitrin. (P.D.) 6th Dose

Rabbit. female.

Wt 2000 gms.

26-11-20

Note

Rise & fall in manometer level.

Rise not well marked - causes no effect on filter which shows marked increase in outflow.

The pressure necessary for perfusion has risen owing to onset of oedema.

1cc Ringer

1cc Pith.

1cc Ringer

Rabbit, female.
wt 2000 gm.
17-2-21.

1cc Pituitrin 3rd Dose.

Controls

Note - Rise and fall \bar{c} Pituitrin. | Increase in Killer rate
- No action \bar{c} Ringer.

1cc Ringer.

Manometer record only

1cc Pituitrin (P.D.) 4th Dose.

Cat, female.

wt. 3500 gm.

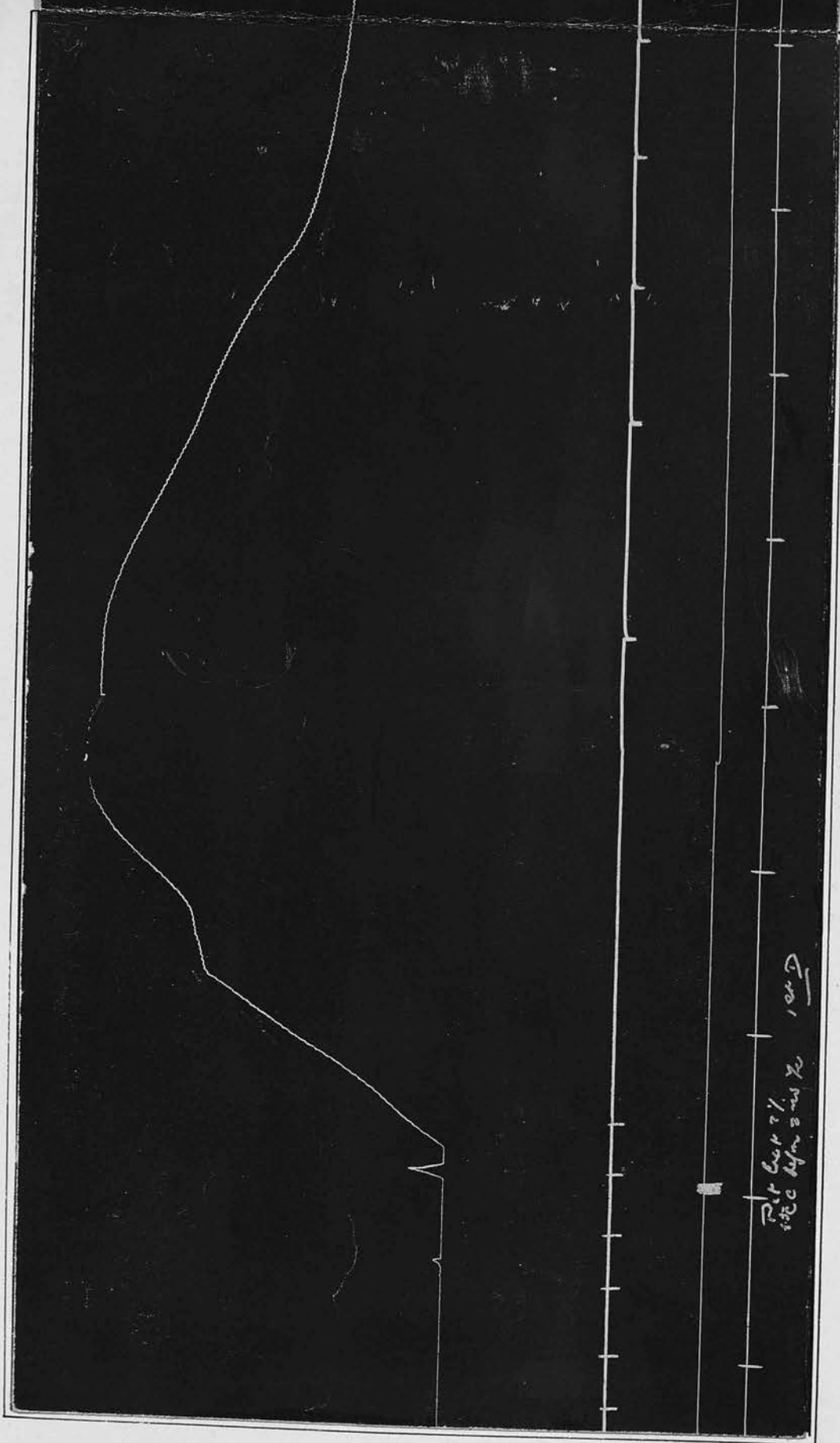
12-11-20

To show that the apparent results of pituitary extracts are not due
to mechanical action

Note - only a sharp rise in fall due to injection

\leftrightarrow 1cc Ringer

45.9



Pit. Exp. 2%
100 D

100 Pit. Exp. 2% - 1st Dose

Rabbit-male.
Wt. 1800 gm.

Note - Rise in manometer level indicating constriction.
Marked slowing of out-flow shown by titler - each hlt = 4.5 cc

091

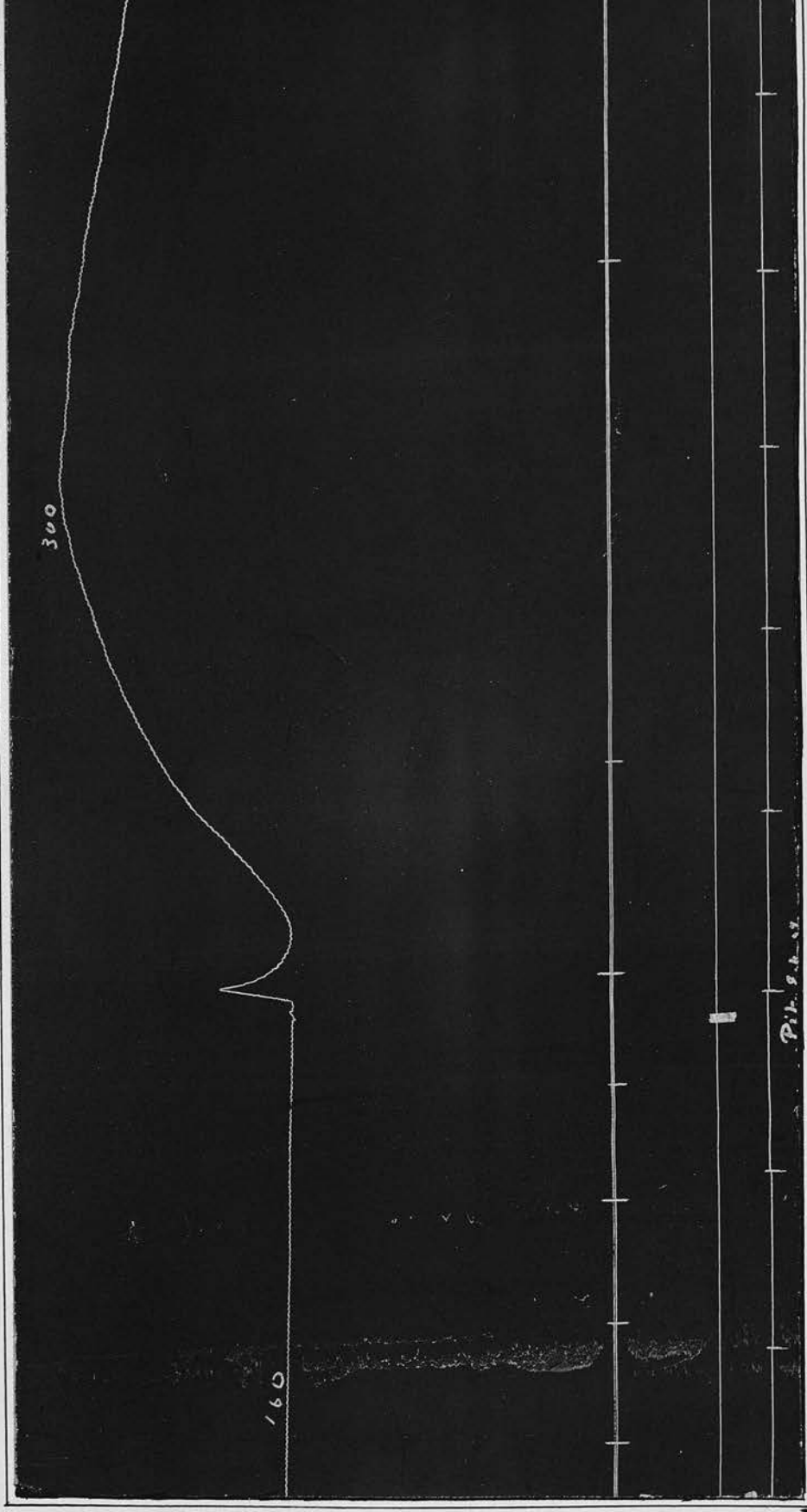
210

With a second and subsequent doses, the result was invariably a short-lived constriction followed by a prolonged dilatation and recovery. Figure 4 may be considered a typical example.

In this instance, it will be seen that the period of constriction is so short that it is not shown by any change in the rate of the tilter, which however clearly shows the dilatation. The effect of the constriction is better seen in figure 3 .

That these effects are not the result of any mechanical stimulus is shown by the controls given in fig.5. So many controls have been carried out that the influence of a mechanical factor can be put out of account. Moreover it was found that the result was exactly the same if the mechanical factor was entirely eliminated by injection near the container, except that the drug was more diluted before it reached the pulmonary vessels and caused therefore less effect, but as it took longer to pass through the pulmonary vessels the effect lasted longer. Owing to the obvious difficulty of reproducing such prolonged results and the additional material required, injection close to the cannula was preferred.

In a few instances the constriction produced by the/
the/



Rabbit - male
 wt 1800 gms.

1cc. Pit. Ext. 4% 6th Dose.

Note - Marked constriction although - 4th Dose.

300

250

230

205

the first dose was followed by a dilatation such as was the usual result with subsequent injections. (Fig. 3)

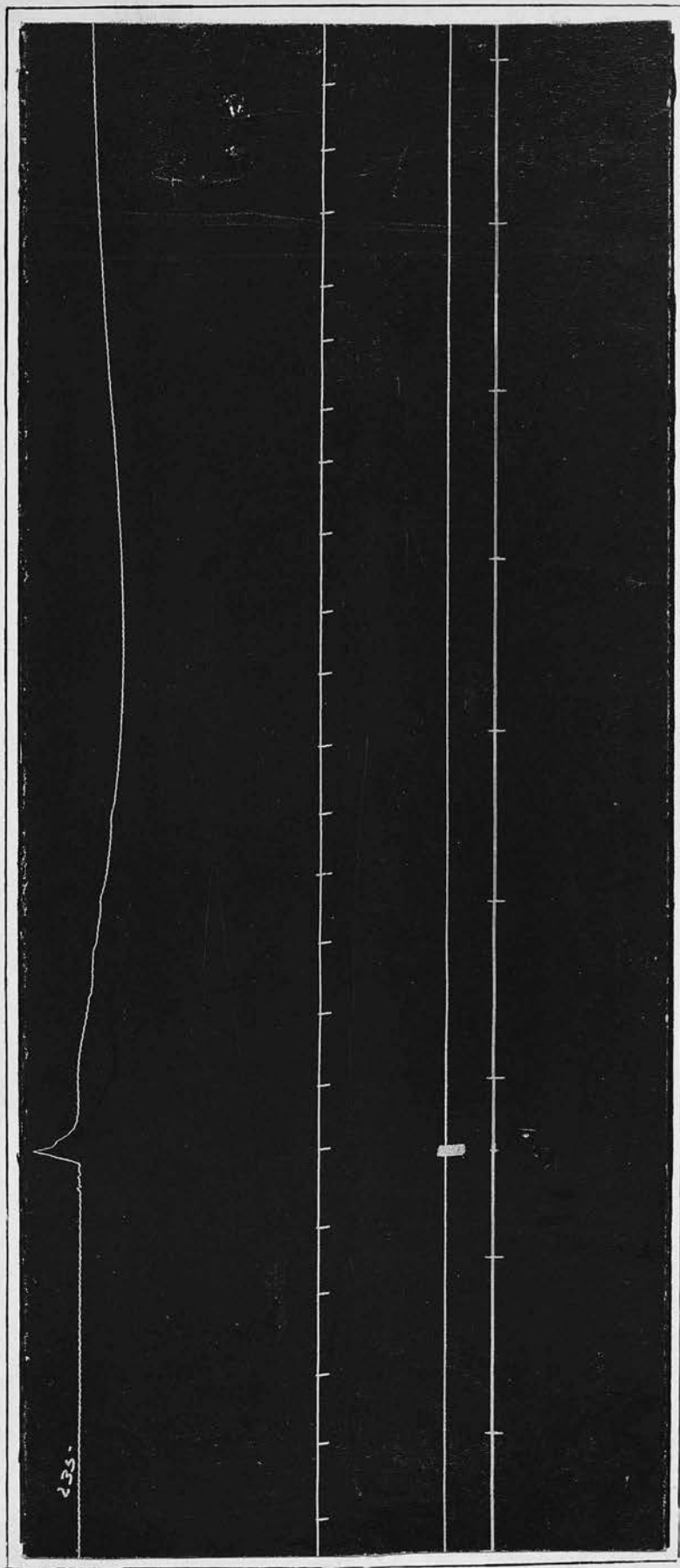
The constrictor and dilator effects of the 2nd and subsequent injections ~~were~~^{were} practically constant.

In only two instances, was there an exception. (Fig. 6 & 7)

In these constriction only could be obtained and as in one case an acid commercial pituitrin was used, and as in the other an extract made with full Ringer-Locke solution, the effect must be considered to be due to idiosyncrasies of the animals, which in both cases were rabbits. Such excessive constriction in rabbits and its "forward" effects in the living animal will be considered later.

With a series of injections the effect of the extracts gradually wore off and it has been noted that the constrictor effect tended to pass off before the dilator. (Fig. 8) When constriction and dilatation occurs it will be noted that the latter is always more marked and it is interesting to note that Cow, in his investigation of rings of arteries, found that when an artery was dilated by pituitary extract the dilatation was proportionately greater than the constriction of other arteries.

of/



From the same
animal as Fig 3

1cc. Pituitrin (P.D.) 5th Dose.

To show gradual cessation of response to Pituitrin.

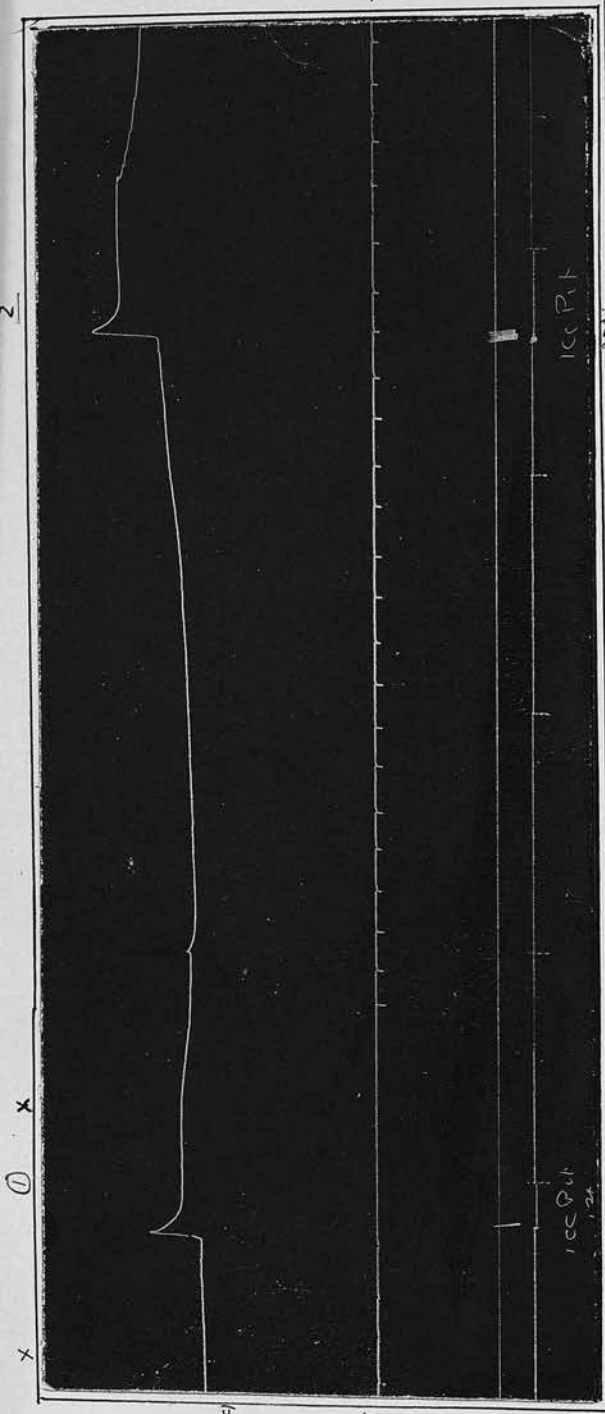
Note - There is no constriction but still
slight dilatation.

Fig - 8

Note Pit & 1 cc out Bicarb Recd gave constriction as did Sod. Bic. alone (cc) while both together A although less of each (see) give a marked dilatation.

T. lter not working well at "X"

Continued to B



1cc Pit + 1cc Sod

1cc Pit

1cc Pit

Continued from A.

at female (post)

B

at female (post)

2100

25-2-21

4cc Pit + 5cc Sod

1cc 1/2 Sod

1cc 1/2 Sod Bic

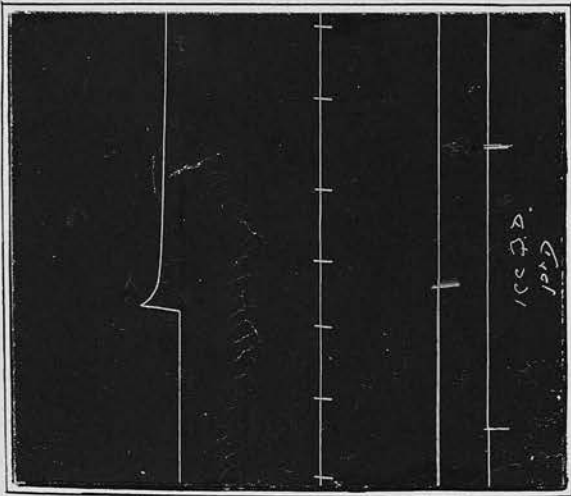
Showing effect of Sodium Bicarbonate in producing dilatation

Fig 9.

Augmentation by
Sodium Bicarbonate

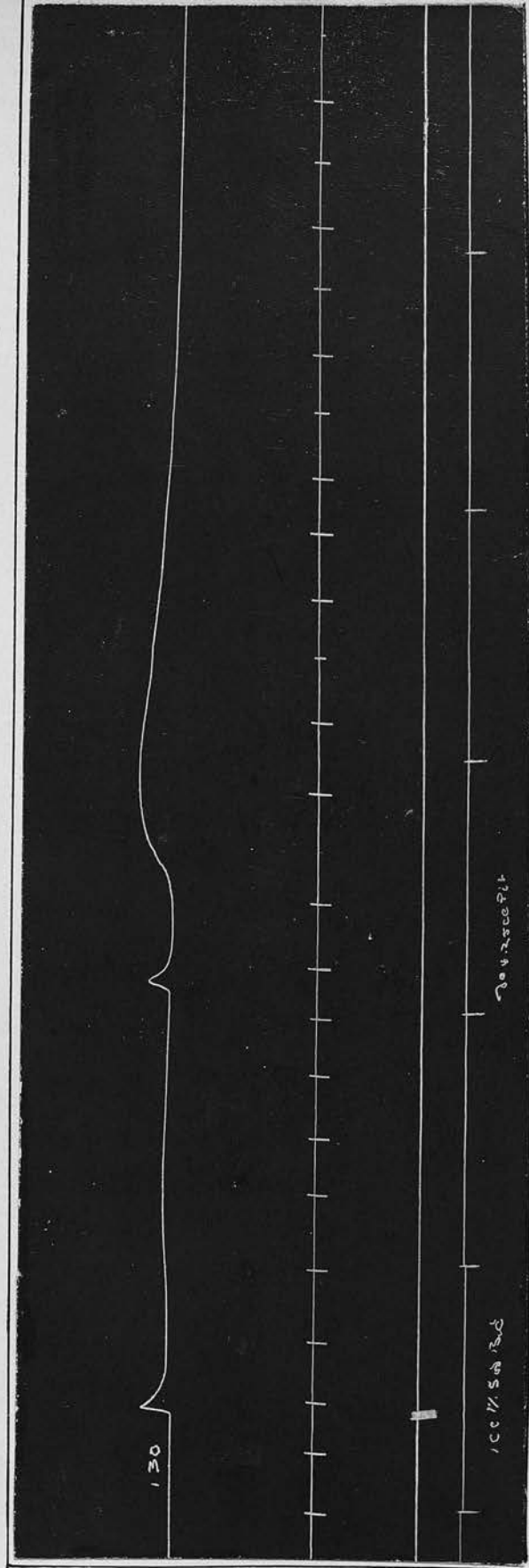
Note - Constriiction with
Pituitrin + Sod Bicarbonate.
but practically no action with
each separately

A



1cc Pituitrin. P.D.
1st Dose

B



Cat (female)
wt. 2000gm
17-8-21.

1cc 1% Sod Bicarb

1cc Sod. Bicarb + 25cc Pituitrin.

7.9.9A.



Cat, female.

Wt. 1700gms.

16-2-21

Action of Sodium Bicarbonate (sat) on Pulmonary Circulation

Note

Marked and prolonged constriction. No dilation

This experiment has been repeated so many times with like result that it may be taken as typical.

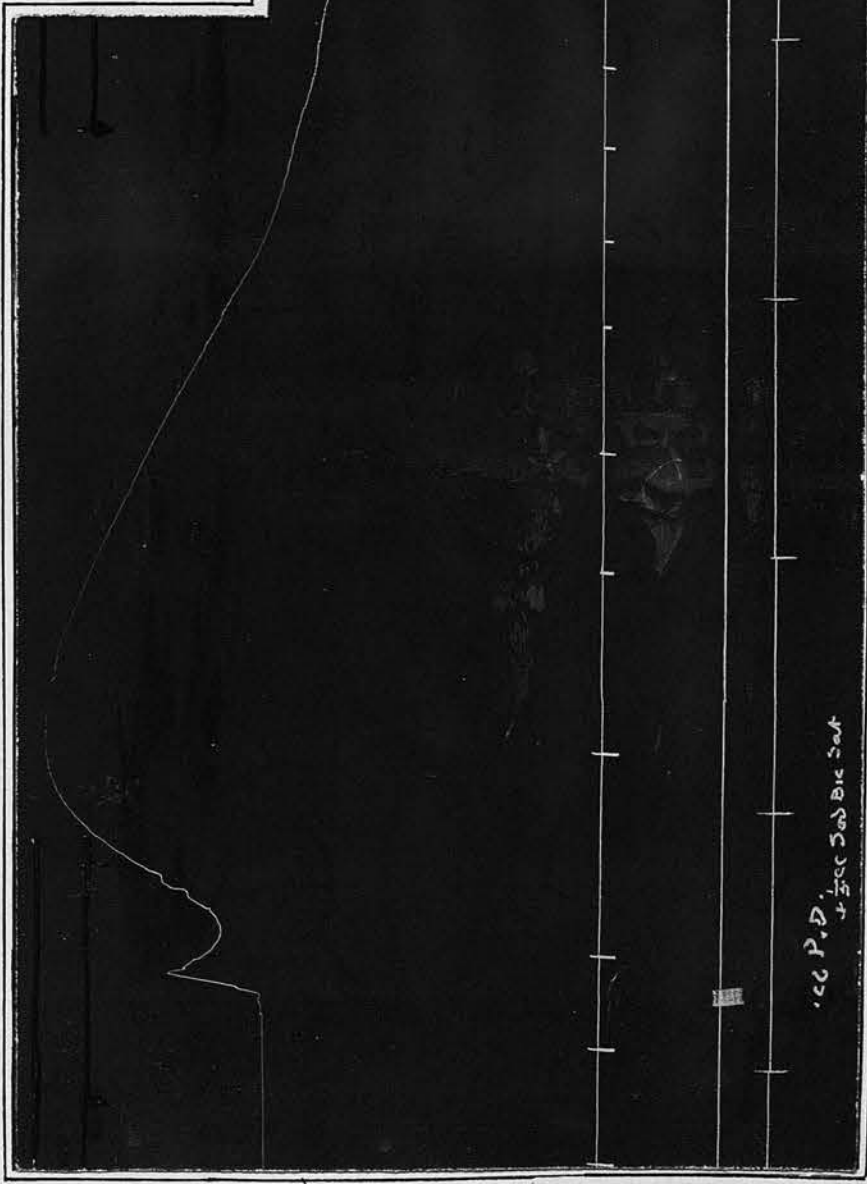
Augmenting effect of sodium bicarbonate on the

action of Pituitary Extract.

Compare - A. action of 1st Dose of Pituitrin.

- B. " " 3rd " " + Sod. Bic.

- C. " " Sodium Bicarbonate alone

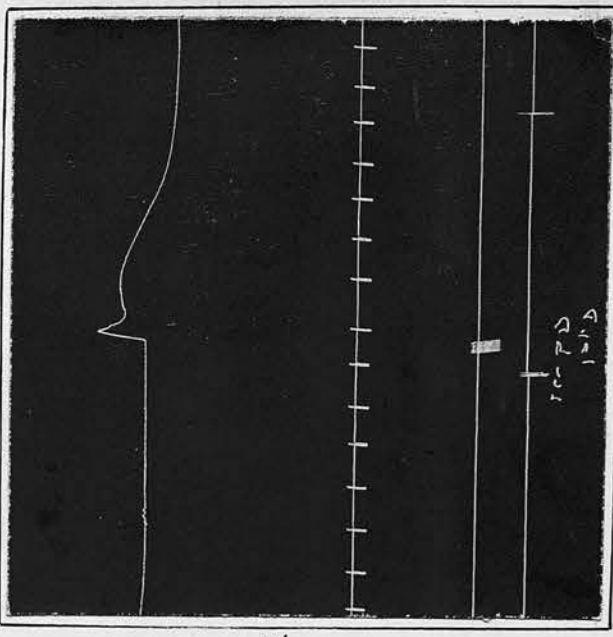


Cat, female
Wt - 1700 gms
16-2-21

1cc Pituitrin (P.D) + 1/2cc Sod. Bic. Sat.

Note - Augmentation of both rise and fall.

A.



1cc Pit. (P.D) 1st Dose.
Both rise and fall given.

Fig 11.

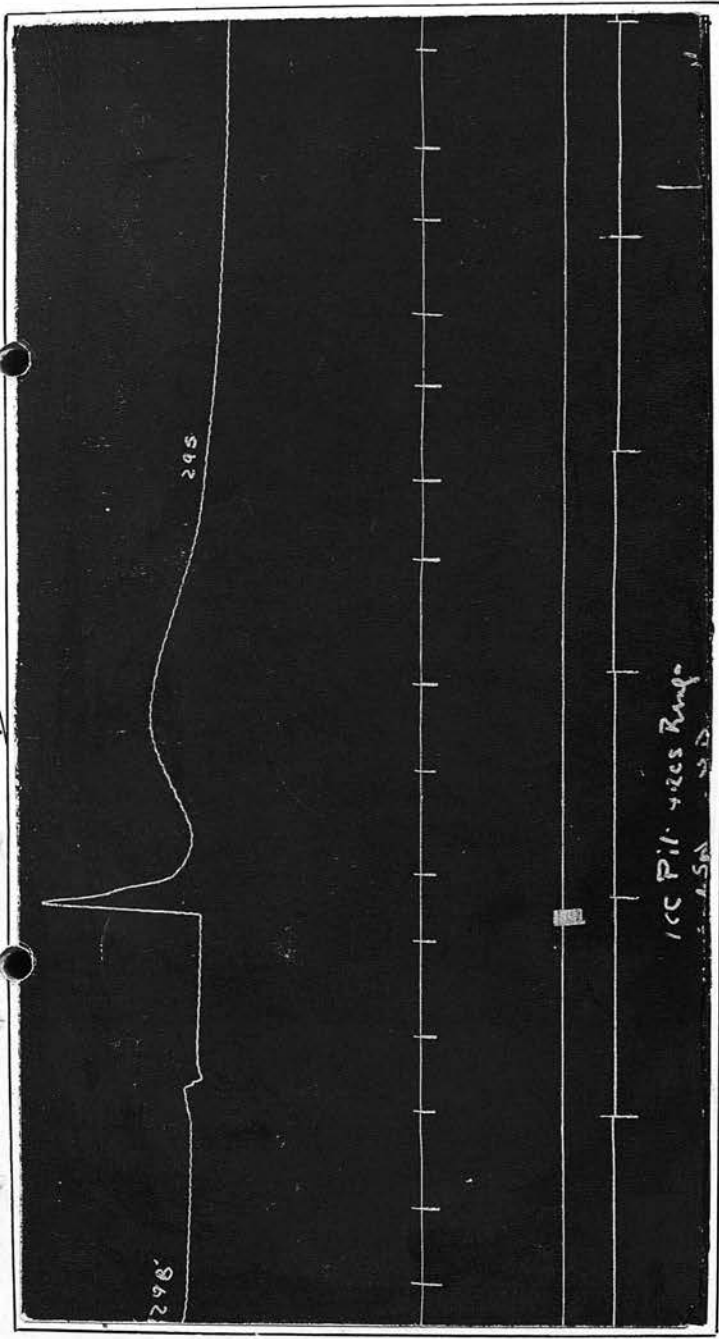
- 1 Action of
Pituitary Extract
without Bicarbonate
 - 2 ditto
with Bicarbonate
- Note in 2
Production of waves
Dilatation.

Shows also
augmentation of effed.
with sodium bicarb.

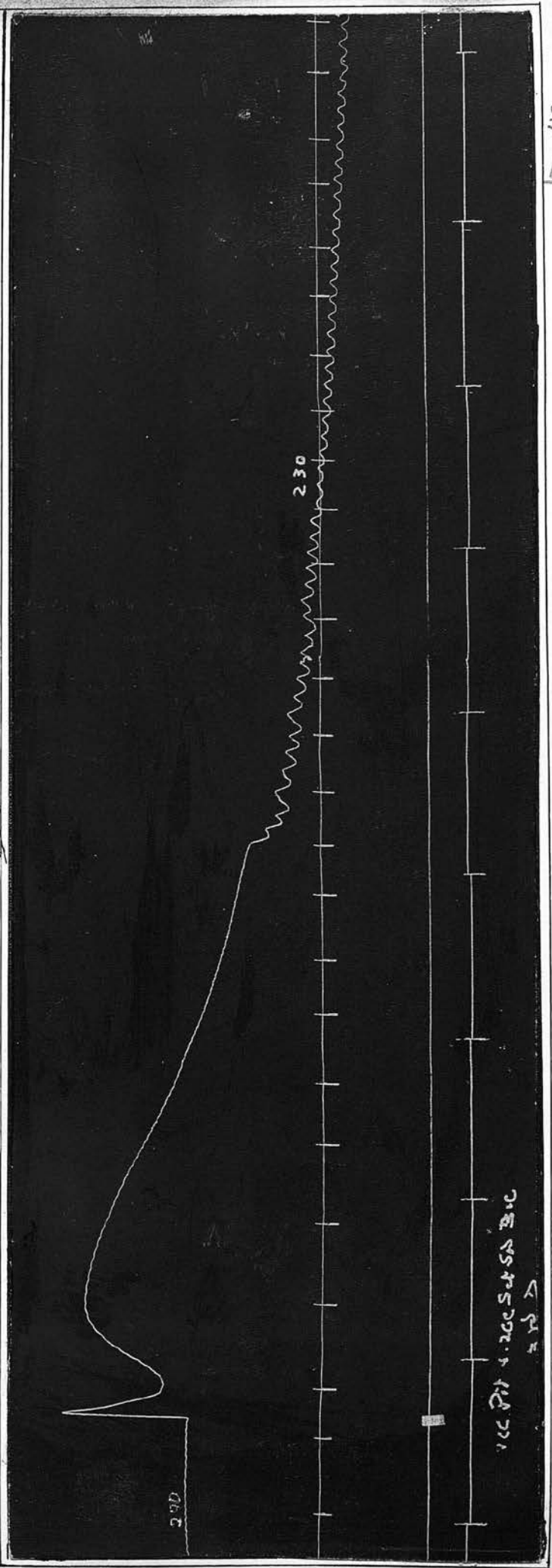
A - 1cc Pit. Ext. - 2 out 500 Bic.
+ .2cc Ringer-Lodge Sol.
2nd Dose

B - 1cc Pit. 2 out 500 Bic.
+ .2cc 500 Bic. sat.
3rd Dose

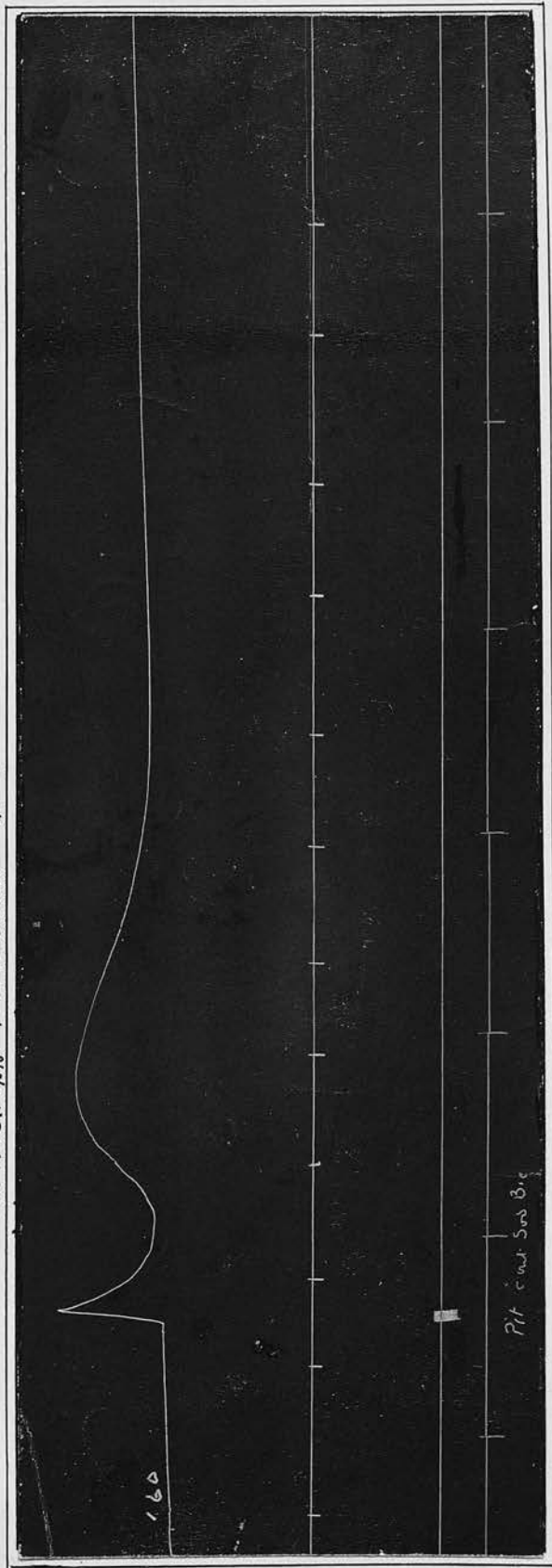
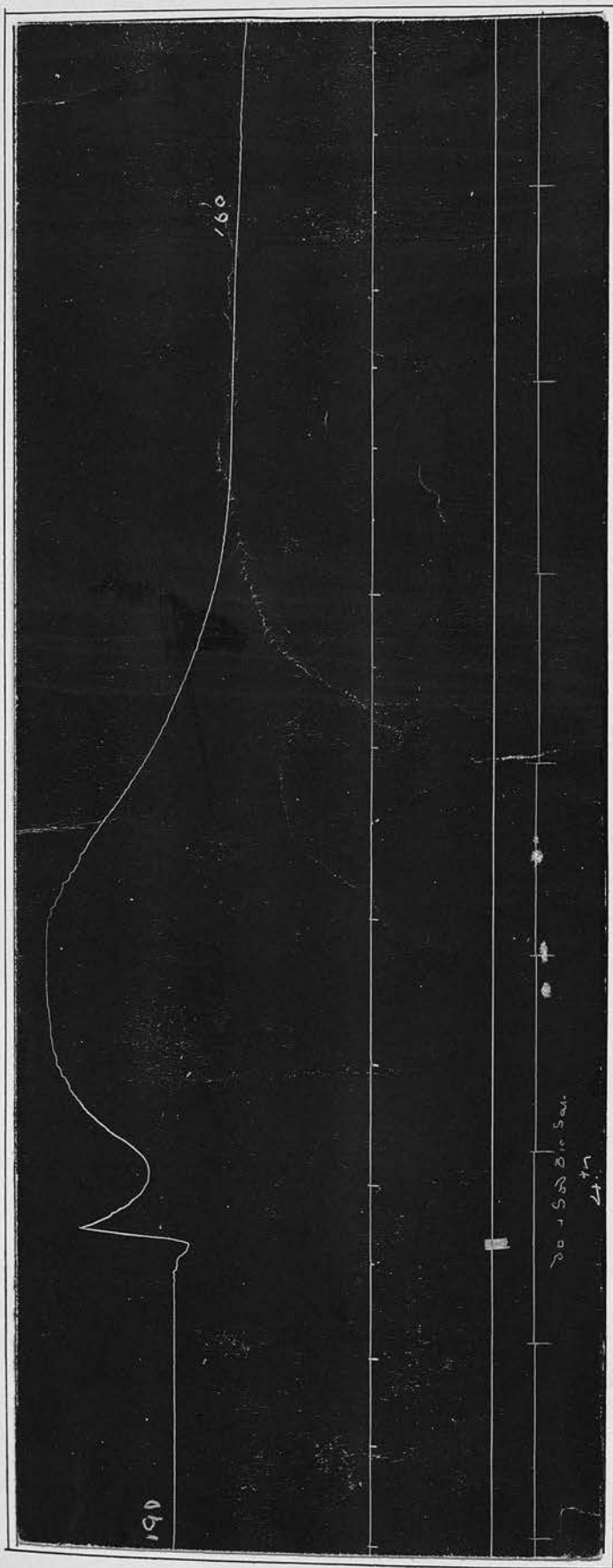
Cat, female.
Wt 1500 - 9-2-21.



1cc Pit. 64t. without 500 Bic + .2cc 2 Ringer - 2nd Dose.



1cc Pit 64t 2 out 500 Bic + .2cc 500 Bic sat. 3rd Dose



Cat. female
Wt. 2000
10-2-21.

Reflexion 2 R. Locke Sol.
without bicarbonate/2.

ICC Pit. Ext. 3 1/2% - 5.14 Dose.
(Ext. Bicarb.)

Note Augmentation of constriction and production of dilatation
with bicarbonate. (cf Fig 10 of bicarbonate alone)

Of special interest is the modifying effect of sodium bicarbonate on the action of pituitary extracts. Figure 9 shows an instance in which .5 cc. of extract and .5 cc. of 1% sodium bicarbonate caused a marked constriction and dilatation, although 1 cc. of each separately caused little effect. (Also Fig.9a)

Sodium bicarbonate not only augments the constrictor action of pituitary extracts, but also the dilator. Figures 10 and 11 show the effect of these substances separately and together in the same animal. Similar results are seen in other animals in figures 12 and 13. A moderate constriction may be considered the normal action of sodium bicarbonate on the pulmonary circulation, but it is well seen that in combination with pituitary not only is the constrictor action more marked, but the relaxation is made more rapid and a marked and prolonged dilatation may be brought about.

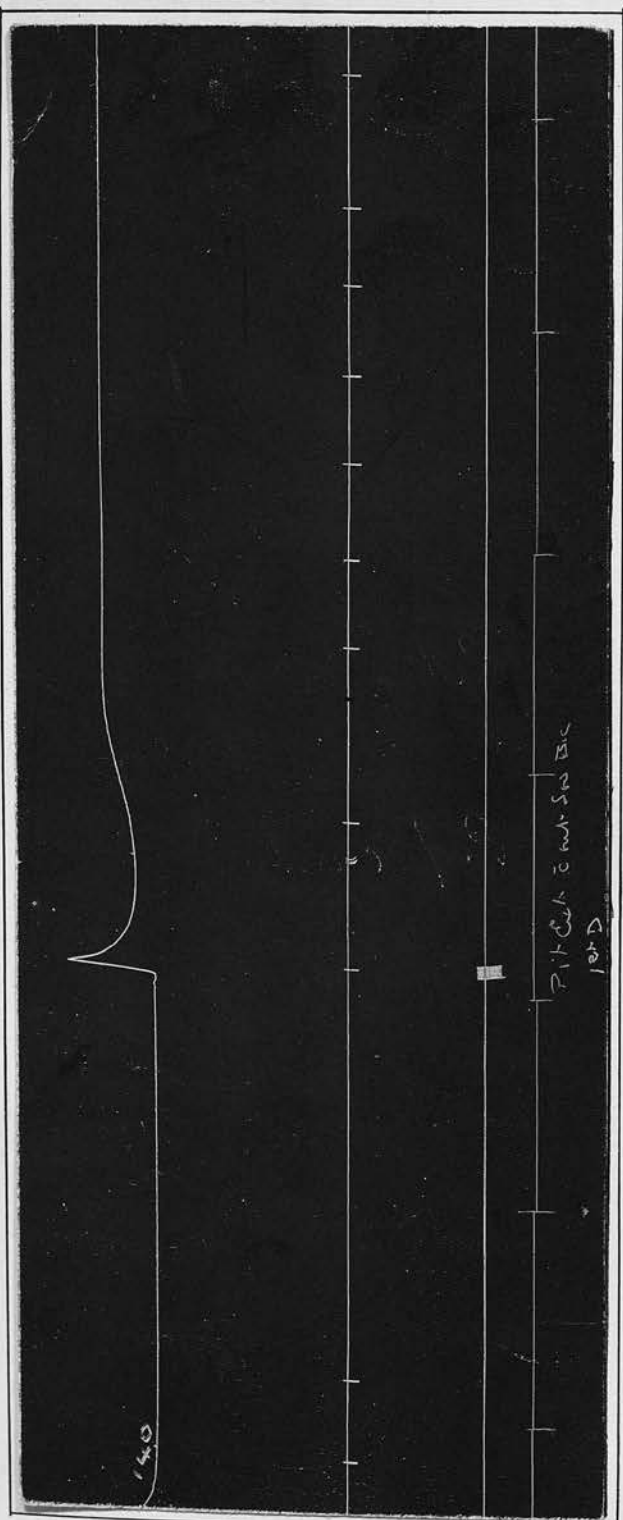
It was found that the bicarbonate was particularly related to the dilator factor in the extracts, indeed it was in this connection that the influence of the bicarbonate was first noted, as instances were found in which extracts of pituitary made with Ringer-Locke solution without bicarbonate caused
a/

Manometer level.

Tiller not working properly

Signal.

Time in minutes



1cc Pit. Ext. 2 out Bicarbonate 1st Dose.

Cat, female

Wt. 2000

Pit. Ext. 3 1/2%

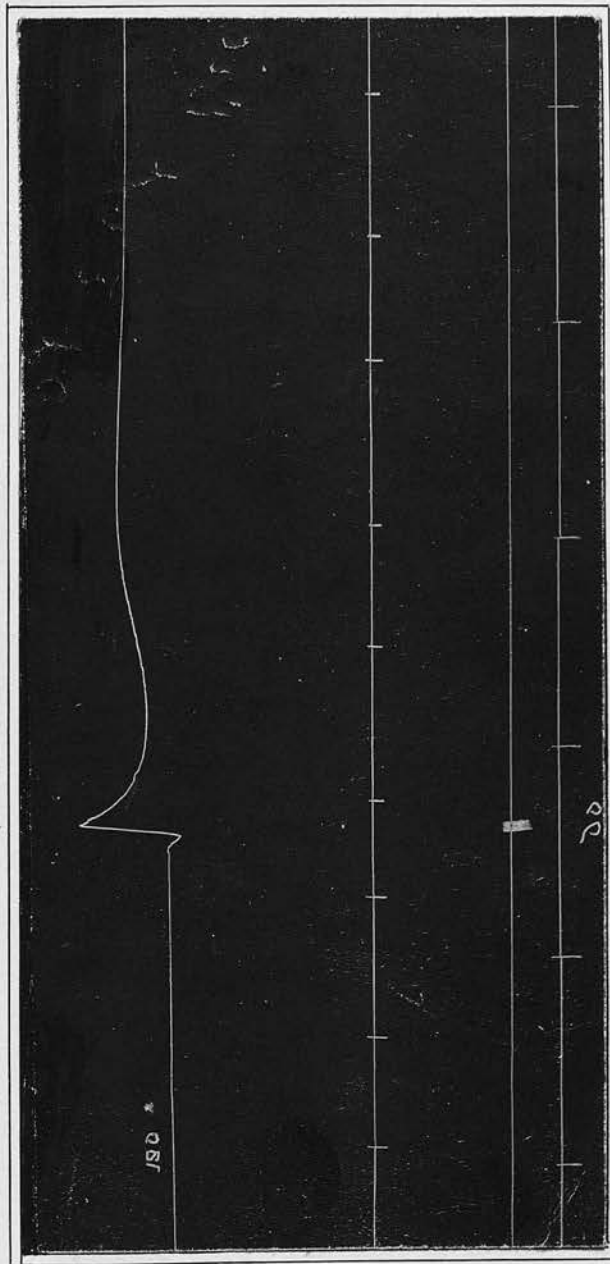
Perfusion with R.L. fluid without Bicarbonate

10-2-21

Note

There is constriction in both cases.

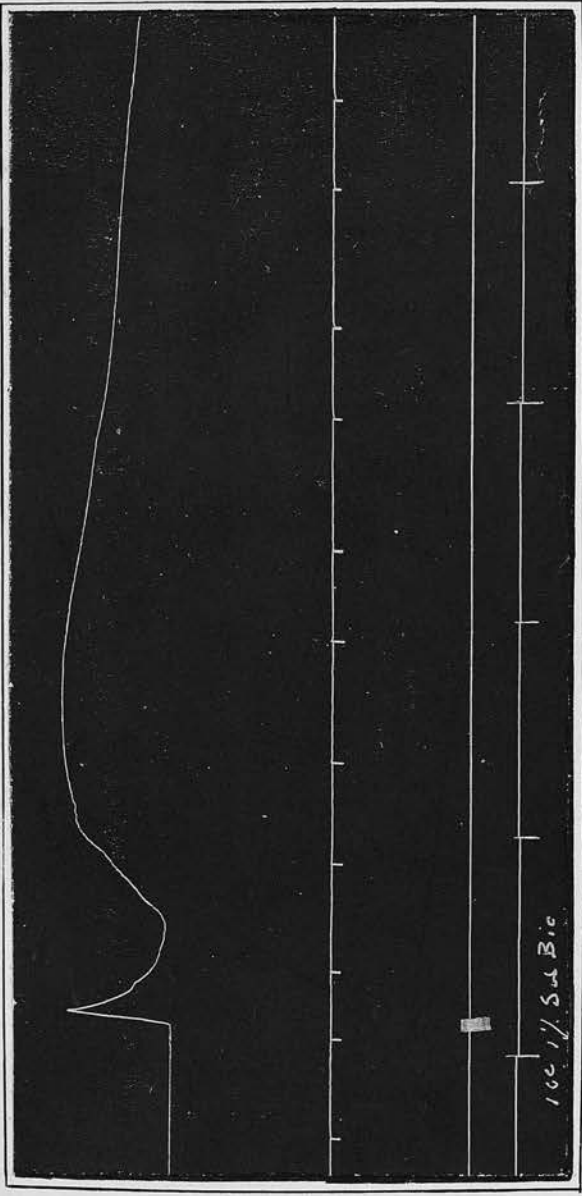
c.f. 4th Dose with Bicarbonate (Fig.)



1cc Pit. Ext. 2 out Bicarbonate 2nd Dose

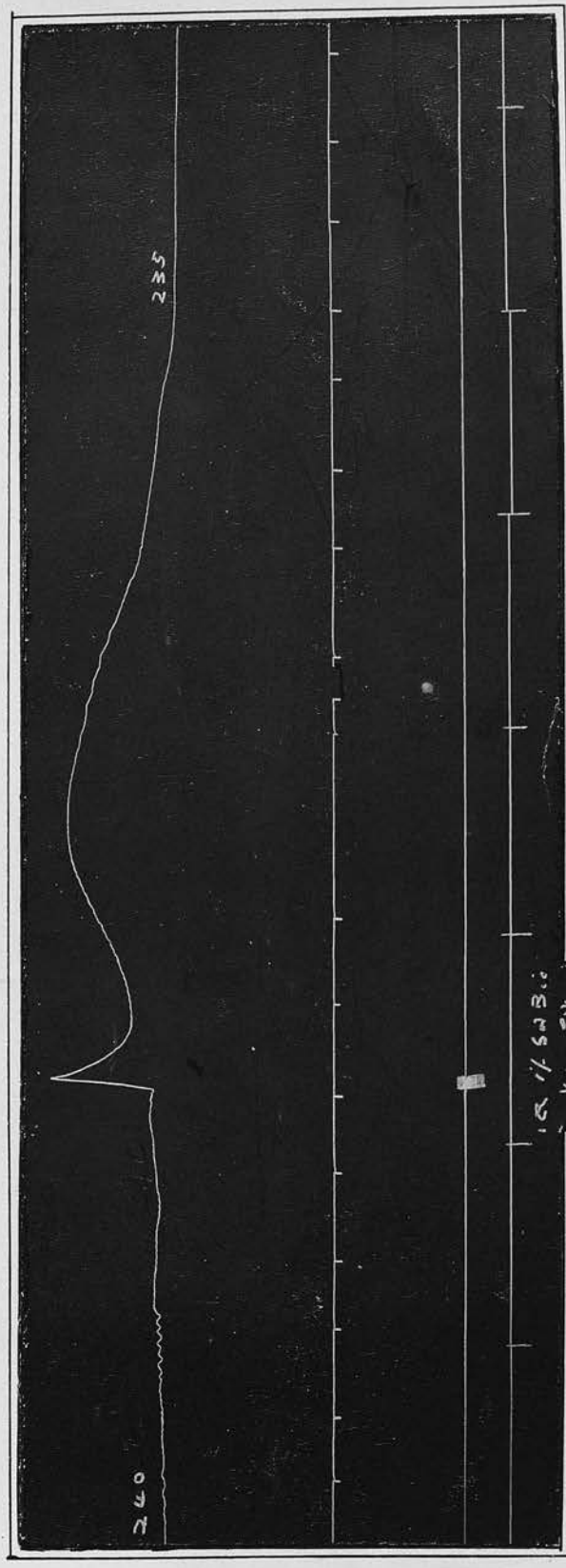
The 2nd Dose gave a similar result.

Note She marked effect
of Pituitrin in
promoting relaxation



1cc 1% Sod. Bic. solution

Cat, female.
Wt. 2000 gms
10-2-21



Perfusion & R.L. without bicarbonate

1cc 1% Sod. Bic. solution
+ 2 minims. Pituitrin.

a constriction only, but if bicarbonate were added a dilatation followed the constriction. (Fig. 13,14,15)

A very large amount of work is necessary before these facts can be clearly understood since, as yet, the natures of the pressor and depressor factor in the pituitary is a matter of considerable debate.

It is however of special interest as Argyle Campbell, working in the same laboratory ten years ago, found that in dealing with rings of the pulmonary artery he obtained constriction or dilatation according to the extracting fluid. He used two solutions of the following composition.-

| <u>A.</u> | | <u>B.</u> | |
|---------------------|-------|-------------|----------------|
| NaCl | .9% | NaCl | .9% |
| KCl | .042% | K Cl | .1% |
| CaCl | .024% | Cal Phosph. | to saturation. |
| Na HCO ₃ | .01% | | |

With A. he obtained dilation, with B constriction. This he attributes possibly to the differences in the Calcium or Potassium contents of these solutions, but apparently he did not consider the difference in alkalinity.

It has already been mentioned that he obtained constriction in his perfusion experiments but, although/

although he extracted with full Ringer's solution, he acidulated to precipitate the protein. He then "carefully neutralised" his solution instead of making it faintly alkaline, like the original Ringer fluid. This fact accounts for the apparent discrepancy between the present research and the work of Argyle Campbell. It has already been noted that the present writer found that extracts made with Ringer Locke solution without bicarbonate were found to give a constriction only. As such a solution is neutral, this finding is really confirmatory of the earlier work of Argyle Campbell.

That arteries are extremely sensitive to differences in hydrogen ion concentration was first pointed out by Severini and by Gaskell, but later Ringer explained the same results as being due to differences in the concentration of the sodium. Quite recently Schi^{ff}~~dt~~ has shown that the action of adrenalin may be considerably modified by hydroxyl ions, indeed he finds that small amount of alkalinity in Ringer-Locke solution is essential to the full action of adrenalin.

The experiments indicated above appear to show that/

that the action of pituitary extracts may also be somehow dependent on reaction of the solution with which they are made. The differences in solubility of the pressor and depressor substances in the pituitary may also be dependent on the same factor.

The whole subject is so enormous and difficult, and so little is known of the chemistry of the active principles of the pituitary that these matters may well be considered outwith the scope of this research.

It is however to be noted that this is the first time any dilator action of pituitary extracts on the pulmonary circulation has been described. This being so, it will do much to confirm the work of Dudley and Dale, who do not consider that the depressor factor in pituitary extracts is histamine, as was contended by Abel and his associates. Histamine has been found by Dale to cause marked constriction of the pulmonary circulation.

Action of pituitary extracts on living animals.

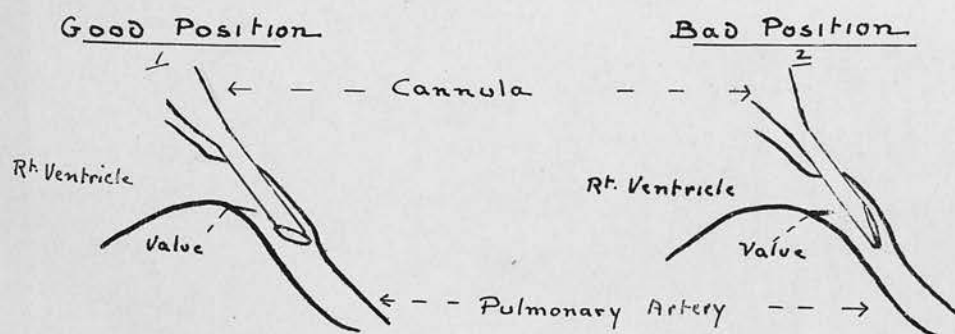
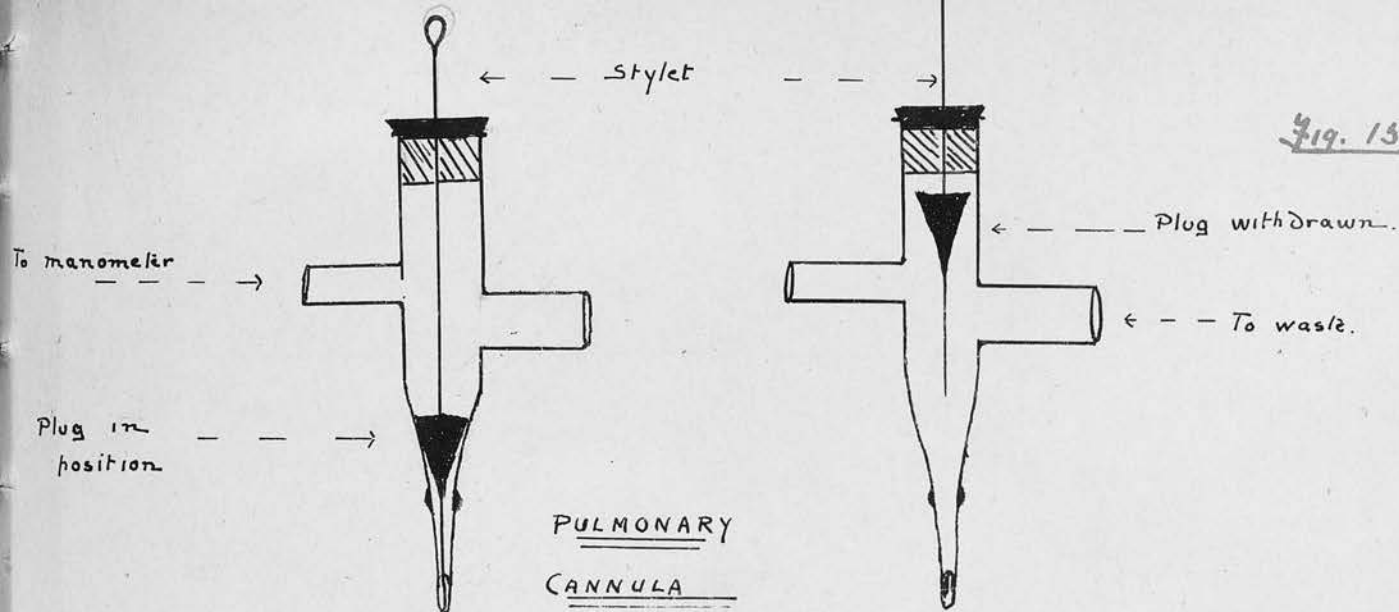
In general the method introduced recently by Sir E. Sharpey Schafer was adopted. Briefly it is as follows, but for further details reference must be made to the original paper.

It consists of introducing a cannula of peculiar construction into the pulmonary artery through the wall of the right ventricle and semilunar valve.

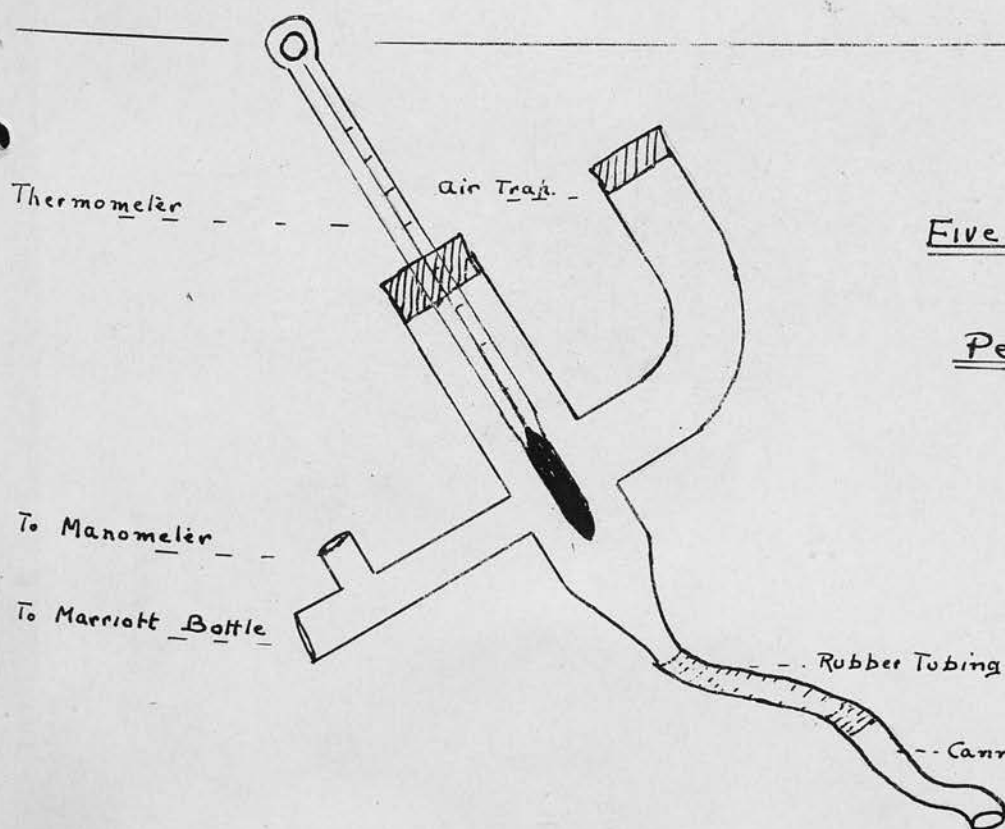
The cannula is shown in fig. 15A. It will be seen that part to be introduced into the artery is fitted with a plug of Chatterton cement to allow of washing without permitting clot or the anticoagulant fluid used to be washed into the pulmonary artery.

Cats and rabbits over 1500 grams in weight were used. The animals were anaesthetised with chloroform but to avoid any action due to its use in the more vital part of the experiments chloral was given to the amount of not more than .5 gram per 1000 grams weight.

Tracheotomy was performed, an injection cannula tied into the external jugular or carotid as desired, and artificial respiration begun by "attaching" the tracheal tube to an intermittent blast of air.



To illustrate proper direction of opening of cannula. "2" is flange to be pressed against arterial wall & occlude



Five Way Cannula
for
Perfusion

One of the carotid arteries was connected with recording mercurial manometer in the usual way and the artery clipped off till required.

After tying a ligature round the sternum at the second interspace to prevent bleeding of the internal mammary arteries, the pectoral muscles were carefully reflected from their origins and the chest opened by cutting through (usually) three ribs close to the sternum. The actual number of ribs cut through depended on the individual animal used. The opening was enlarged by blunt dissection and its sides held apart with hooks, every effort being made to interfere with the pleura as little as possible. It was found advantageous to keep this intact if possible, although in some animals this was no easy matter.

The pericardium was now opened, the right ventricle seized with mouse-tooth forceps about a centimeter from the semilunar valve, and a purse-string suture placed in position round the forceps. A cut was made with the scissors into the right ventricle close to the forceps and the cannula immediately introduced through the opening into the pulmonary artery by way of the pulmonary valve. The purse string was then tied to hold the cannula in/
in/

in position, the ends being further tied round one of the lateral branches of the cannula to avoid the possibility of its being pulled out. It might be noted that making a cut into the right ventricle was preferred to that of merely cutting the epicardium and pushing the cannula through the muscle and endocardium as originally described. Instances occurred where the endocardium appeared to have been stripped off and in which the cannula was blocked from the beginning, presumably the result of tissue being driven into it—in spite of the stylet—during process of pushing it through the muscle.

The chest was then sewn up, care being taken to keep the cannula in its proper alignment with the pulmonary artery. In relation to this latter point, the bevelling of the cannula had to be remembered, otherwise it could easily be obstructed by pressure of the opening against the wall of the artery (Fig . 15A.5.)

During completion of the closure of the chest, the lungs were distended by a continuous air blast to ensure subsequent negative pressure. Artificial respiration was then removed and the animal allowed to breathe naturally.

A double tambour stethograph connected with a tambour/

tambour was applied to the upper part of the abdomen to record respirations, the clip removed from the carotid artery, the plug withdrawn in the pulmonary cannula and simultaneous tracings taken of the pulmonary and carotid pressures. (Fig. 16A)

Over 40 such experiments were carried out in this way. The commercial pituitrin made by Parke Davies & Martindale and extracts made by myself according to the method described above, were used.

In actual fact the experiments on the living animals were carried out before the perfusion experiments and as the possibility of a dilatation following a constriction in the pulmonary circuit had not been considered, the results obtained were so diverse and ununderstandable that the whole investigation appeared so fruitless that it was almost abandoned.

When, however, the numerous variable factors are taken into consideration and it is appreciated that a constriction followed by a dilatation is a common result of the action of pituitrin - a fact shown by the perfusion experiments but not hitherto described - the interpretation of the results seen in the living animals becomes a much easier problem.

These variable factors may be summarised thus, Cardiac variation, central vasomotor changes, spontaneous/

spontaneous changes in the calibre of the arteries themselves, the influence of one circulation on the other by backward or forward action, and the well known idiosyncrasies of individual animals.

In the light of what has already been said regarding the sensitiveness of pituitary extracts to sodium bicarbonate, it seems quite reasonable to believe that the hydrogen ion concentration of the blood and of the tissues may play some part in the production of these idiosyncrasies.

Pituitary extracts have not any marked action on the heart as has already been shown by previous investigators. That this is the case is evidenced by the results of this research. If it were so it would be shown presumably by a parallelism between the aortic and pulmonary curves. It will be noted that such parallelism is almost conspicuous by its absence. A tracing is shown. (Fig. 42)

The possibility of the two sides of the heart being differently affected has to be considered, but as the different effect so frequently coincides with the results observed in perfusion experiments, this possibility does not appear to be an important one.

For the most part the only influence of spontaneous/

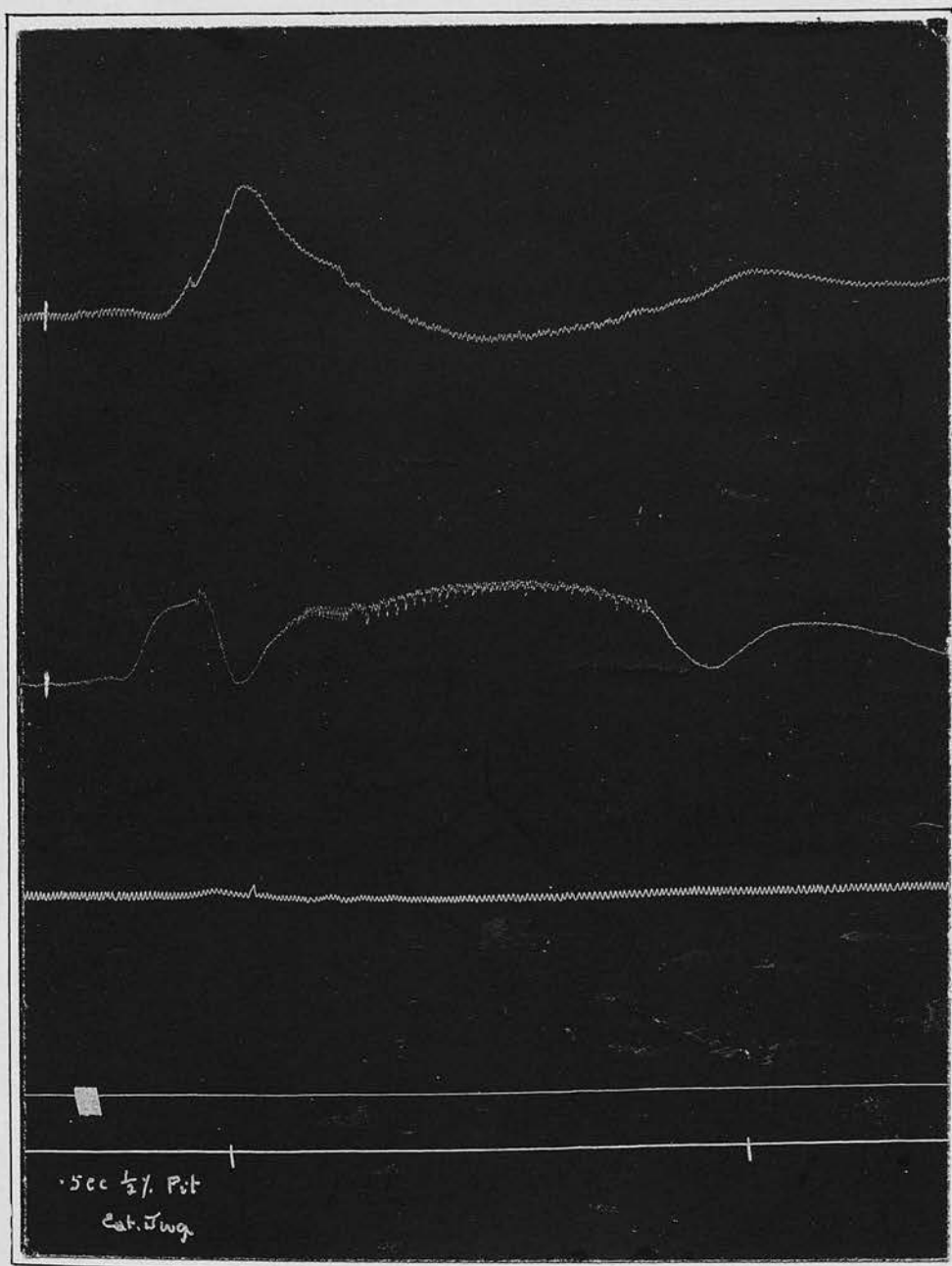
spontaneous changes in the calibre of the vessels may be considered to the small variations and waves which appear in some tracings. (Fig. 40+41)

The possibility of the influence of one system upon the other by a "backward" or "forward" action will be considered later: suffice it to say meantime that although the effect of backward action - that is effect by backward pressure - can be neglected in animals in which the left ventricle and mitral valve are physiologically sufficient, that is especially it seems in rabbits some effect by "forward action", is seen in those animals which are very sensitive to the autocoid. Further reference will be made to these influences later.

In all cases where simultaneous points have been put on since the varnishing of the tracings, their position has been accurately determined with dividers from the nearest points actually taken.

The majority of animals react to the first dose, but in only about half the experiments could any definite result be obtained with subsequent doses. A few animals appeared to be insensitive to the action of the autocoid altogether.

The effect of the first dose was usually to cause a marked rise in the pulmonary blood-pressure (Figs. 20, 21, 22, 24, 27) and in a few instances the rise was/



Rabbit, male.
Wt. 2200 gms
chl. .5 gr.
22-9-20.

↑ .5cc Pit. Est $\frac{1}{2}\%$ 1st into vein.

EXCEPTION

Note

Rise and fall in pulmonary

Aortic show a fall due to "forward" action.

The pulmonary fall does not correspond to aortic rise

and is produced by dilatation of pulmonary vessels.

Simultaneous points

GENERAL ARRANGEMENT OF APPARATUS

IN

EXPERIMENTS ON LIVING ANIMALS

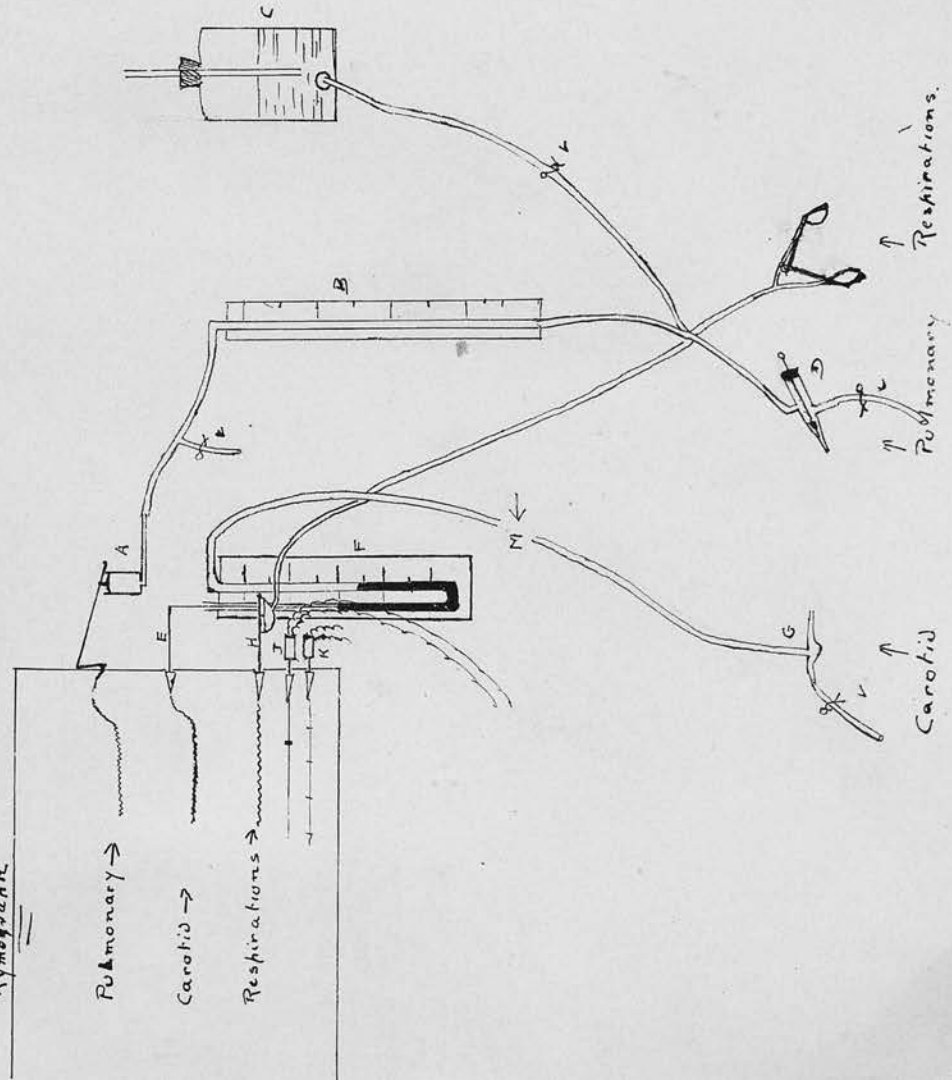
(Schematic diagrammatic)

Kymograph

Pulmonary →

Carotid →

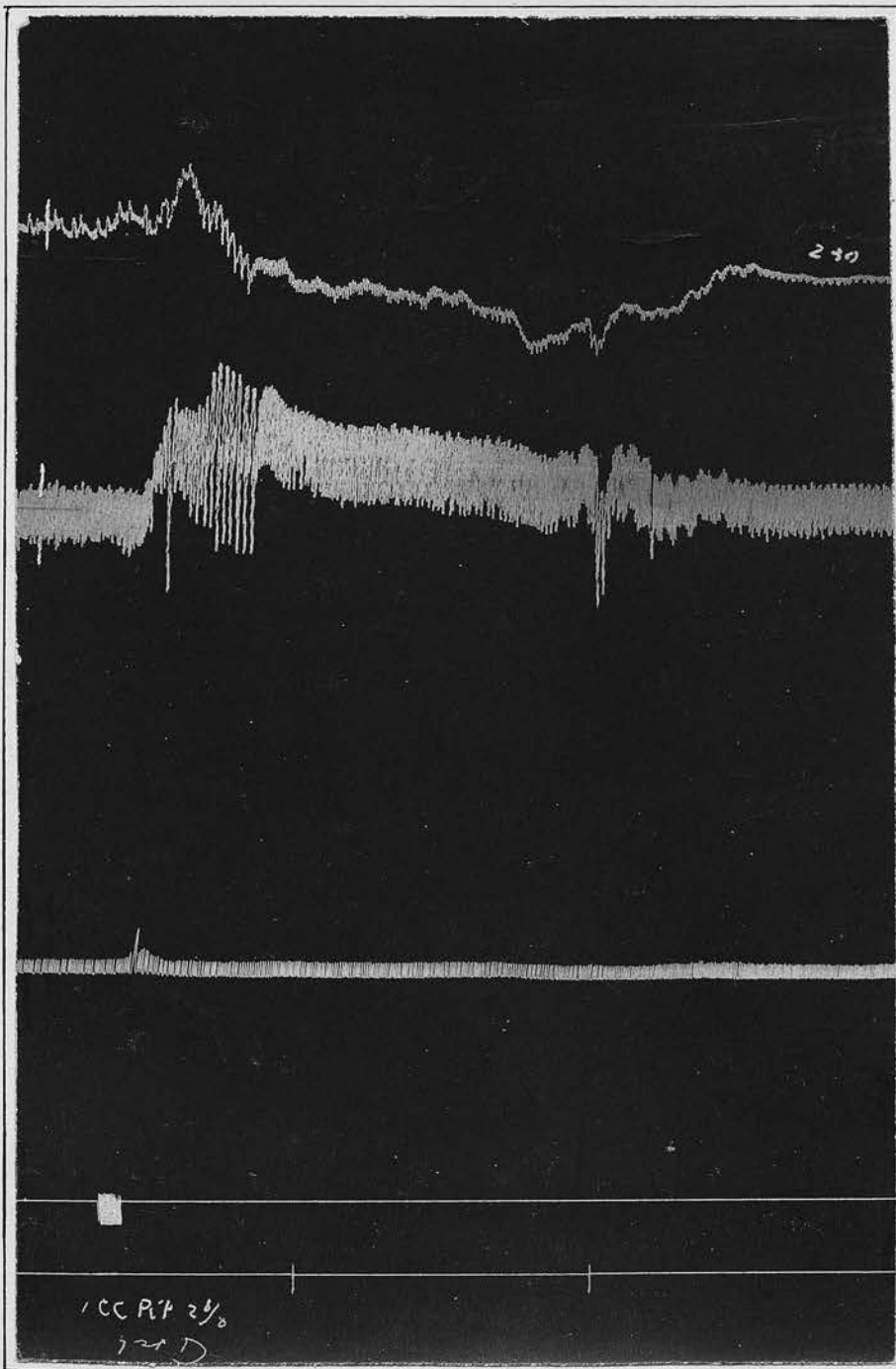
Respirations →



LETTER REFERENCES

- A - Ellis Piston Recorder.
- B - Water Manometer.
- C - Mariotte Bottle 2 ft. for wash.
- D - Pulmonary Cannula.
- E - Recording Float.
- F - Mercurial Manometer.
- G - Carotid Cannula.
- H } Tamboors for
- I } respirations.
- J - Hand worked, electro-magnetic sign.
- K - Time marker.
- L - Clip.
- M - Pressure Bottle here.

Fig. 16A.



Pulmonary b.p.

Aortic b.p.

Respirations

Signal

Time in minutes

Cat, female, preg.
wt 3400 gms.
Ch. Hyp. 75gms.
13 : 1 : 21

1cc Pit 2%
2nd D

Simultaneous points - ↑ 1cc. Pit. Est. 2%. 1st Dose into vein.

Note - Rise of short duration in pulmonary followed by prolonged fall. (C.F. Fig) Similar to perfusion results.
Typical rise in aortic

was of short duration and followed by a dilatation. (Figs. 16 and 17).

With subsequent doses there was a great variety of results. In by far the largest proportion of experiments there was no reaction at all. In several there was a rise of short duration followed by a more prolonged fall (Figs. 18 and 19a). *also 19c.* Occasionally there was a fall only (Fig. 19A) and in these cases where the first dose had caused a very marked rise, the subsequent doses also caused a rise of less extent. (Fig. 20). It is also to be noted that several instances occurred in which, although the second or even the third dose caused no definite result, the subsequent doses caused a rise followed by a fall. (Fig. 19). ^{19c.} The animals gradually became less sensitive to the extracts.

The question at once arises as - how much the results indicated above are due to "forward" and "backward" action.

Backward Action. That this does not occur has already been shown by Sharpey Schafer and Lim and by Bradford and Dean, but further and conclusive evidence can readily be shown. If the rise in the pulmonary pressure were due to a rise in the aortic it would be/

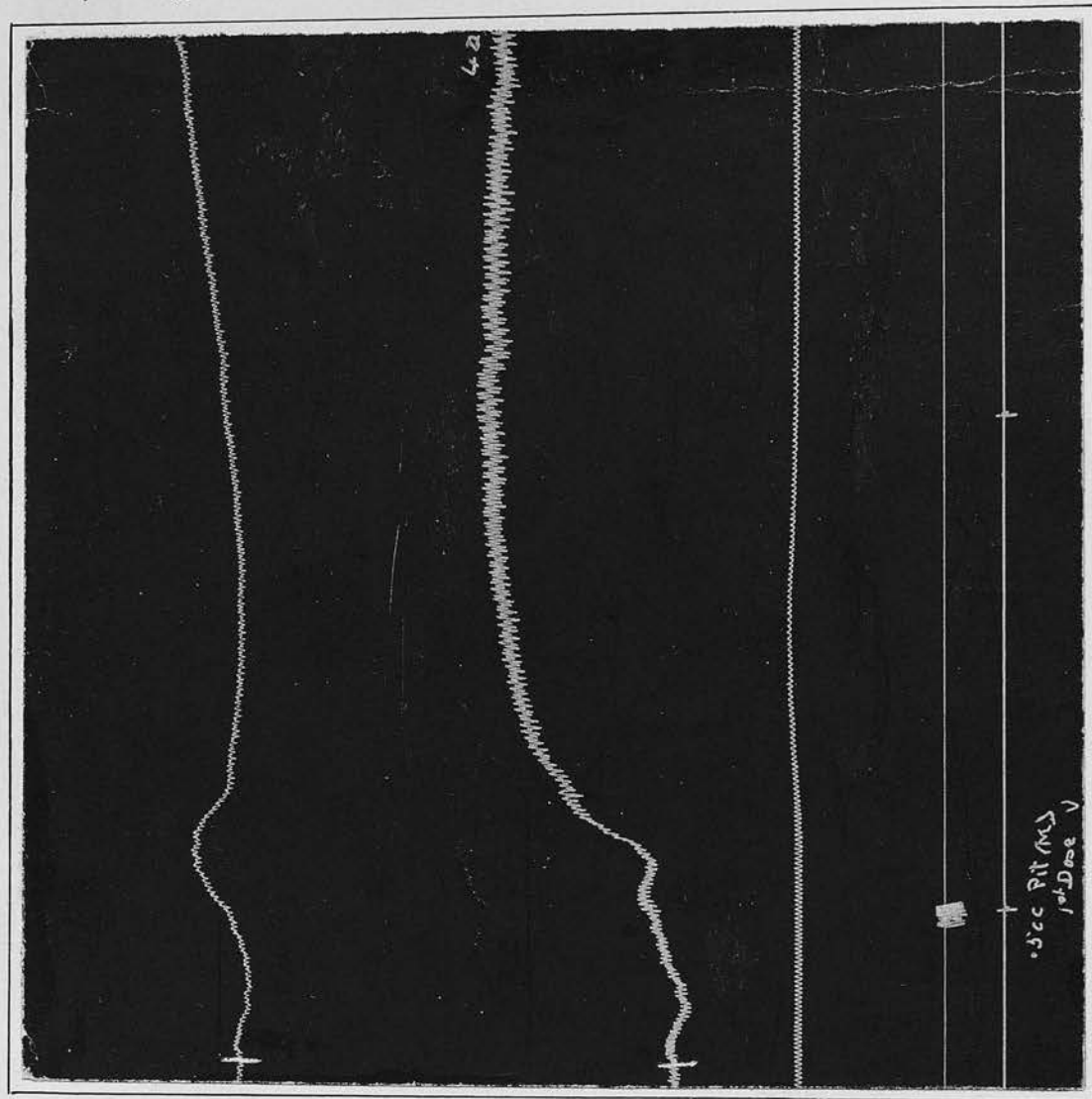
Pulmonary blood pressure
75 mm Hg.

Aortic blood pressure
80 mm Hg.

Respirations.

Signal.

Time in minutes



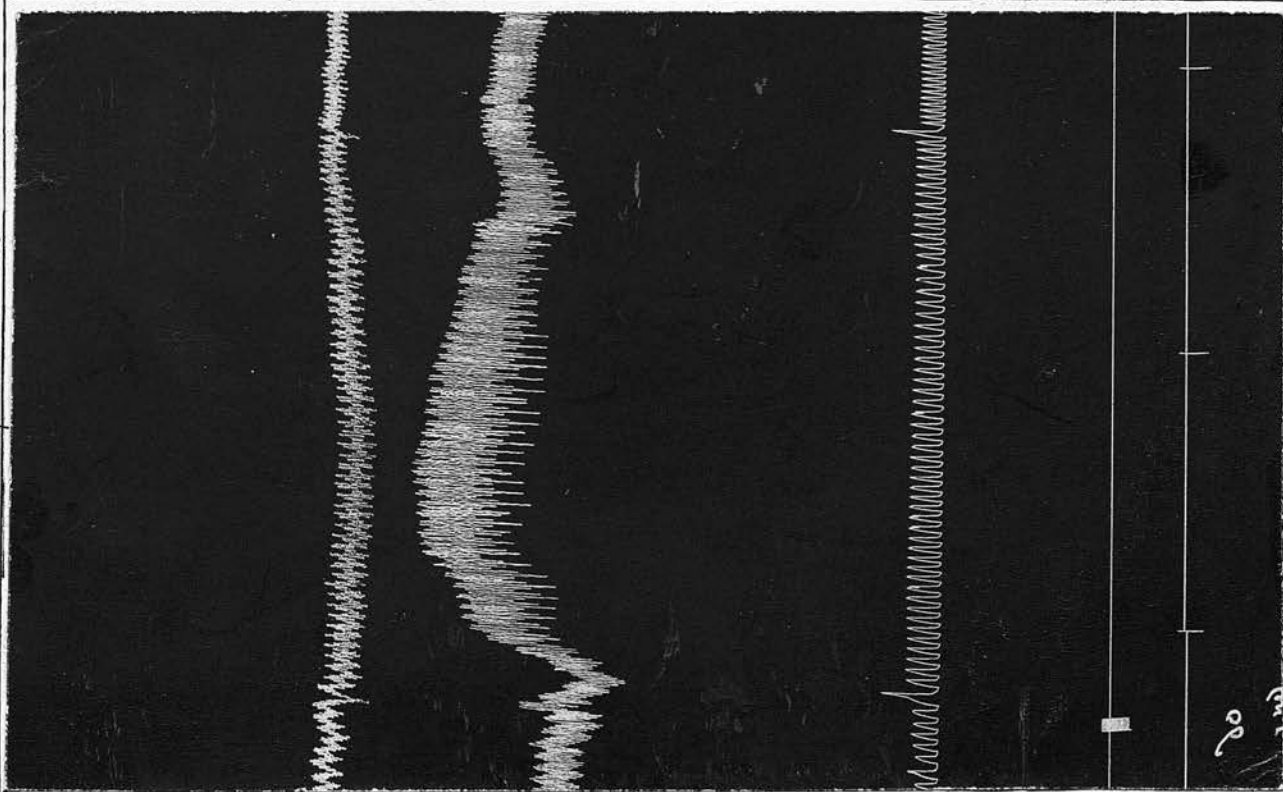
Rabbit, male
Wt. 2350 gm.
Ch Hys. 49m

↑ Simultaneous points measured by dividers from nearest. —
Noli Marked rise in both, commencing in Pulmonary
5cc Pit (M) 1st Dose V

Fig. 21

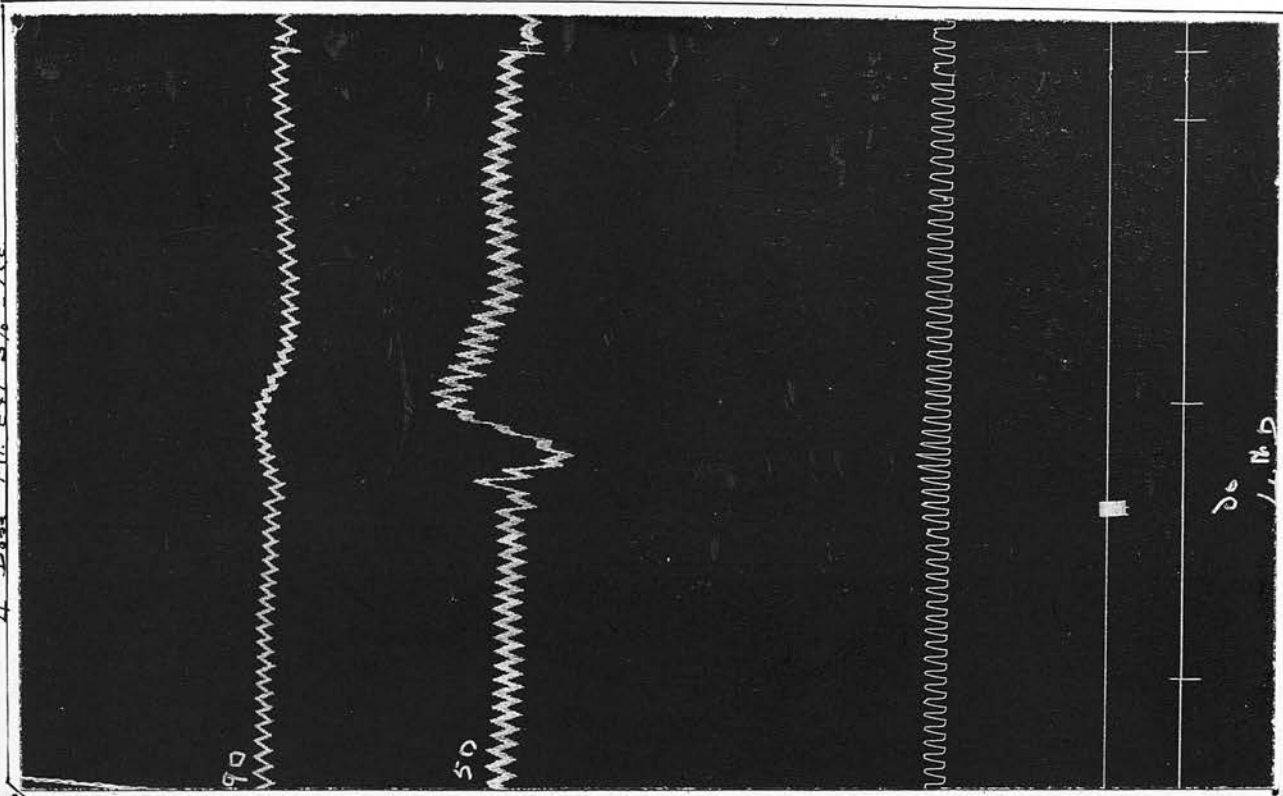
2nd Dose Pituitary Extract 3% - 1cc.

4th Dose Pit. Ext. 3% - 1cc.



A

Cat, male
Wt. 3000gms
Chloral Hydrate
1gm.
19:1:21



Simultaneous points
B - Pulmonary - rise succeeded by fall
Aortic - fall succeeded by rise
Note - B. Aortic fall occurs first, & pulmonary rise before aortic

EFFECT OF SUB-
SEQUENT DOSES.

A - Pulmonary fall (slight)
Aortic fall succeeded by rise
Both arterial injections.

2nd

4th

Do
1st

Respirations

Signal.

Time in minutes

Pulmonary
Pressure = 90 mm H₂O

Aortic
Pressure = 100 mm Hg

Fig. 19.
A & B

28

be expected that the latter would ~~rise~~^{occur} first on intravenous injection. Figs. 21, 25 shows that this is not so.

Furthermore, a rise in the pulmonary is not infrequently very much greater than that in the aortic^{Fig 20} and indeed as is seen in figure ~~22B~~²³. which is from the same animal as figure 22B a rise in the pulmonary may occur during a slight fall in the aortic which is the common result in that pressure of a second or subsequent doses of pituitary extracts. Also Fig. 24 and 28A, B.

Forward Action. That the rise in the pulmonary could possibly be^{due} to a dilatation of the systemic arterioles and the allowing of more blood to reach the right side of the heart is of course negatived by the rise which occurs in both commonly as the result of a first dose. Moreover with intravenous injection the rise of the pulmonary occurs before the fall in the systemic. (Fig. 20) Also as is seen from figure 23 the fall in systemic is usually of short duration, while the rise in the pulmonary may be prolonged.

The possibility of the fall in the pulmonary pressure being due to a lessening of the amount of blood passing to the right side of the heart, the result/

EFFECT OF
"FORWARD ACTION"

Note - Great rise in pulmonary
2nd dose causing (fall
in aortic probably a
lessening of the aortic rise
2nd dose aortic
effect typical unaffected by
small rise in pulmonary.

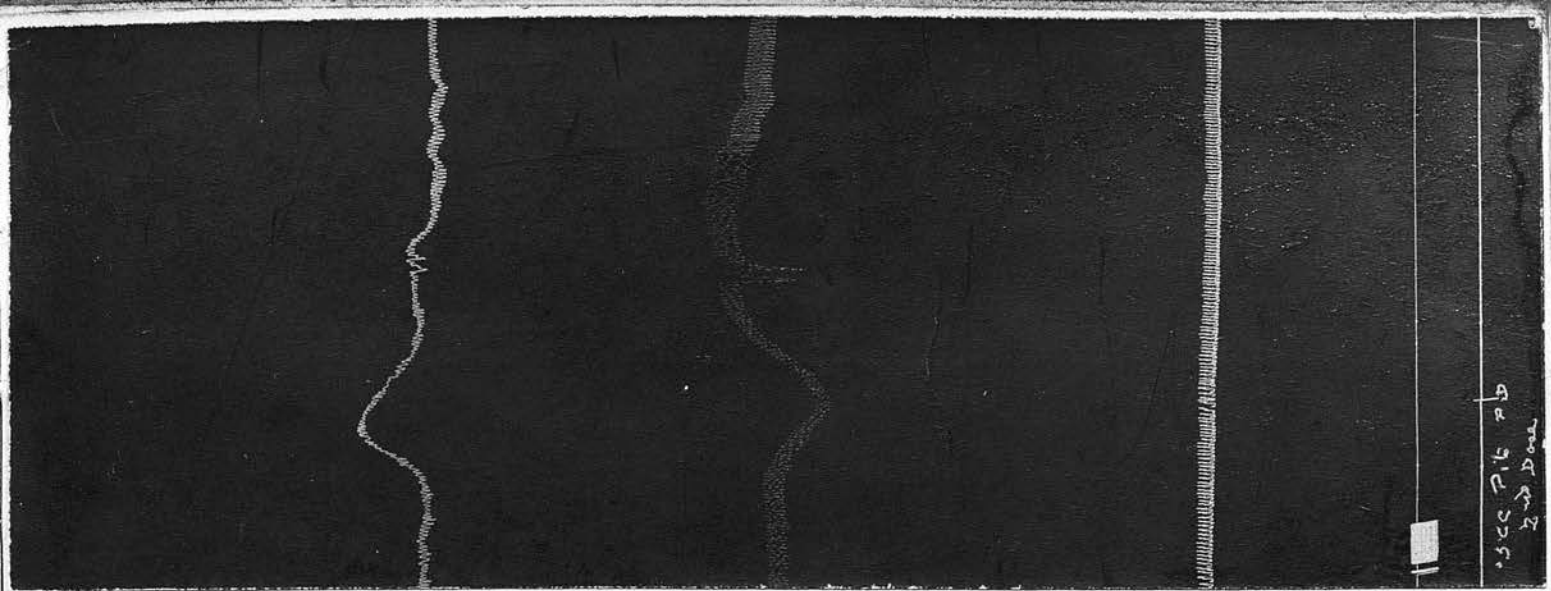
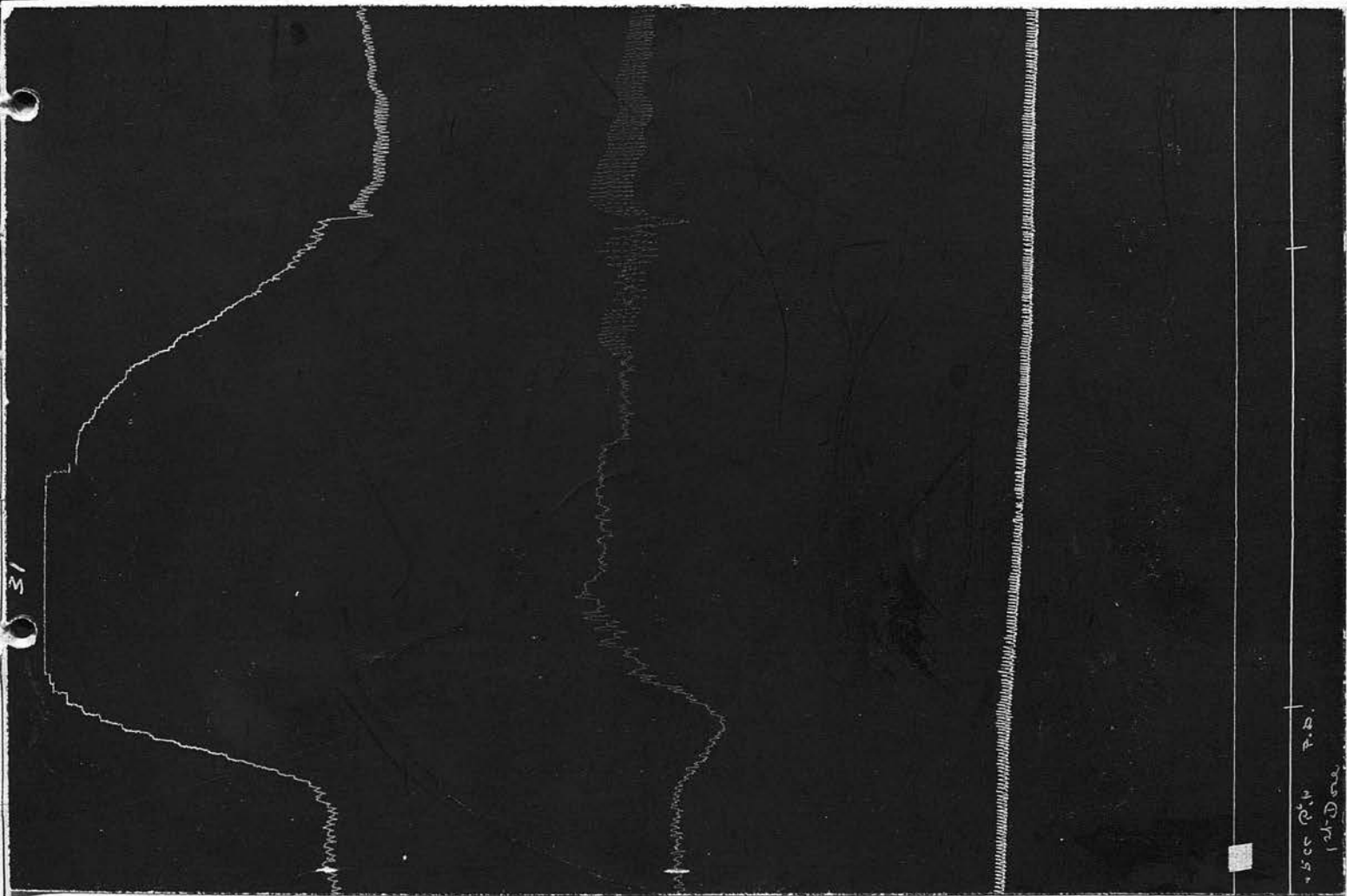
A - 1cc. Pit. (P.D. Co) 1st dose
into vein

B - 2nd dose ditto.

Cat, male
Wt 2850 gms.
Chl Hy2. .75 gm
9:7:20

Fig 20

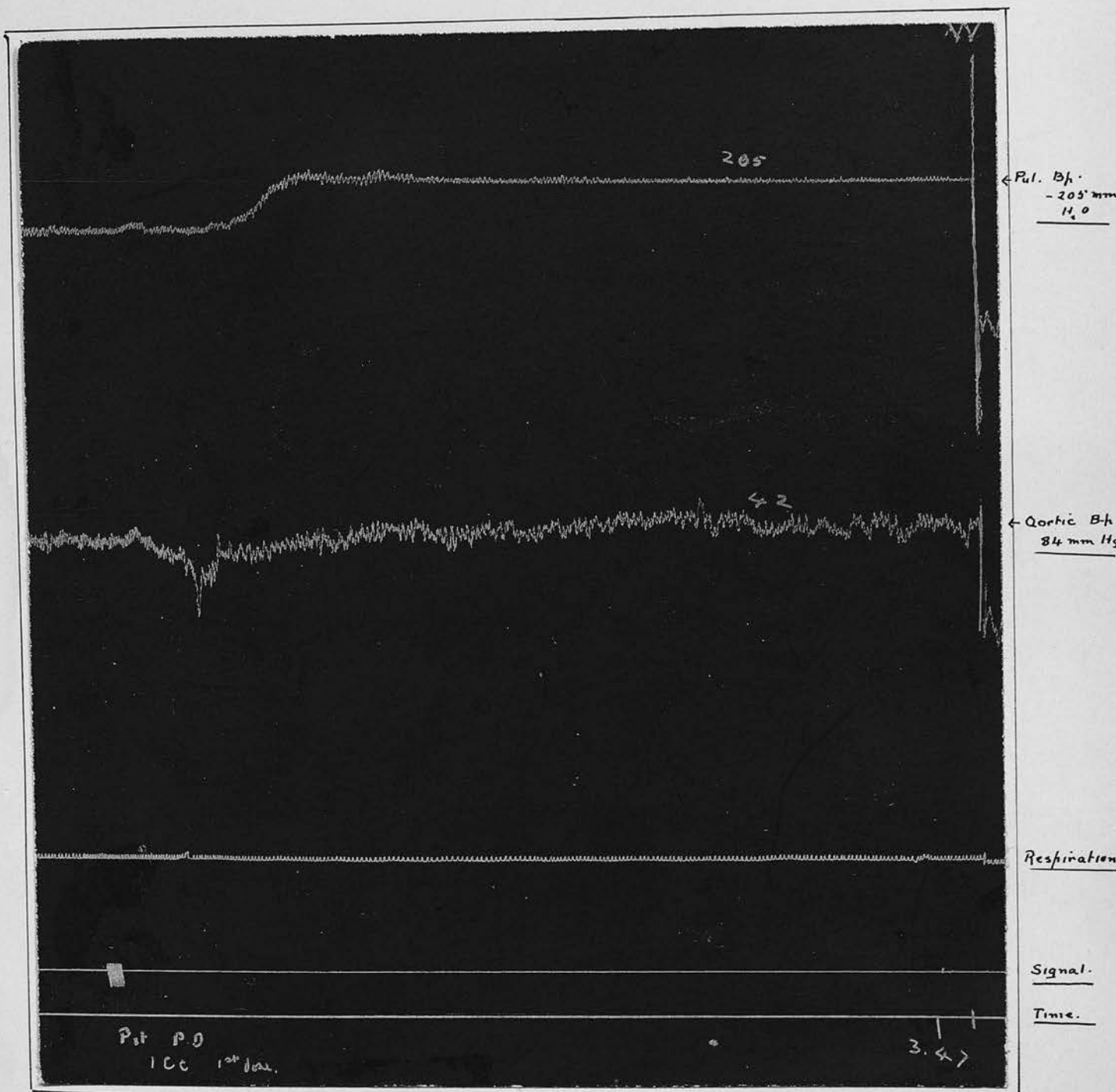
28



1st Dose
2nd Dose

1st Dose
2nd Dose

Fig. 24.



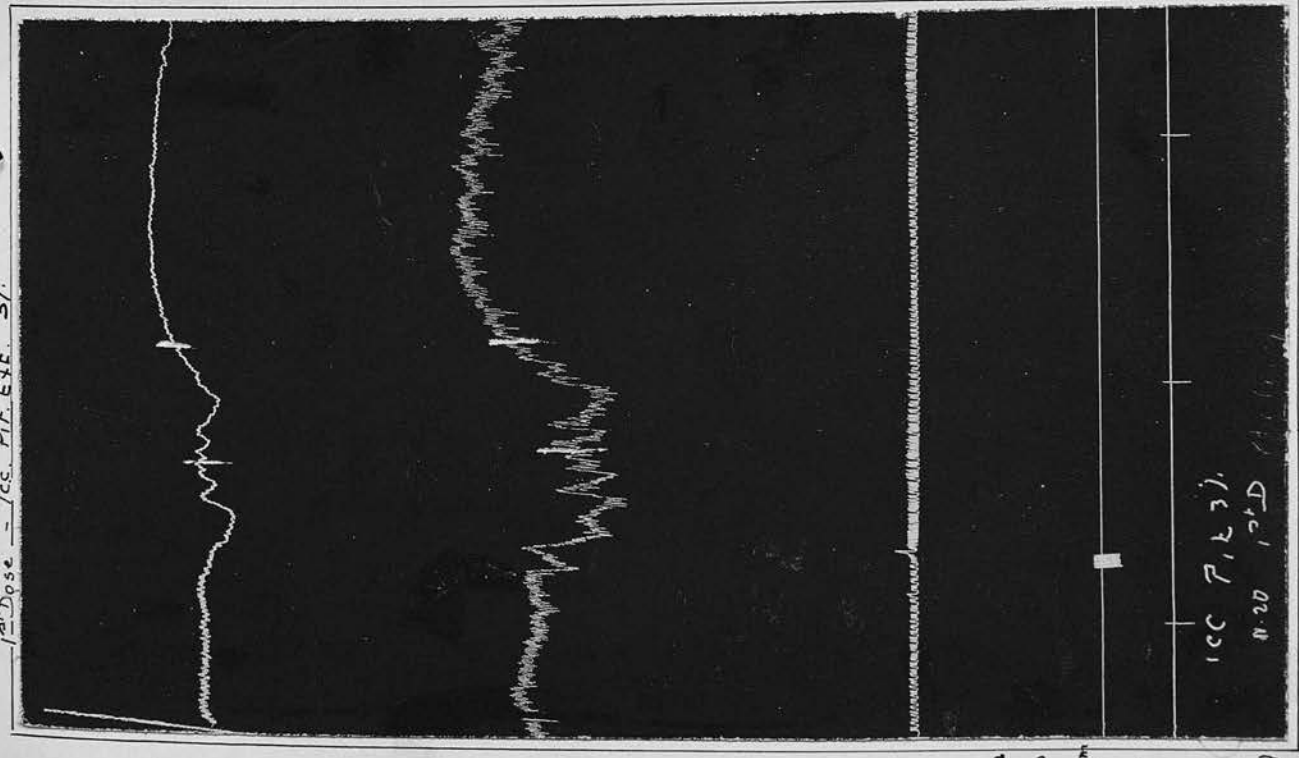
t, female.
2100
4.5 gr
2:10:20

1 C.C. Pituitrin (P.D. & Co) 1st Dose int Vein.

↑ Simultaneous
points

Note Rise in pulmonary, little change in aortic
Slight initial quickening of respirations.

1st Dose - 1cc. Pit. Ext. 3%.

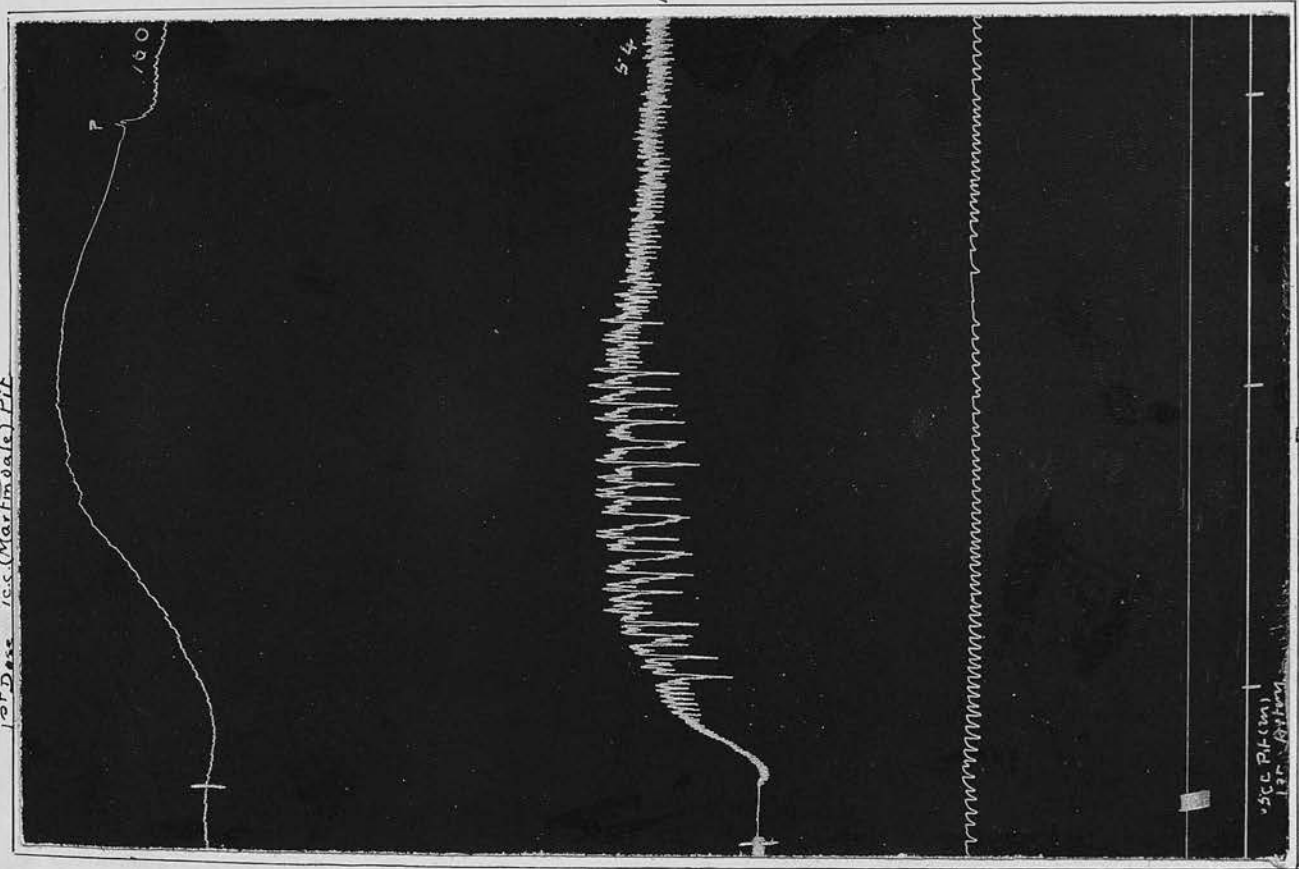


Cat, male
Wt - 2000
Ch. Hy - 49m
19:11:21

1cc Pit. (3).
8-20 1st D

A

1st Dose 1cc. (Marrindale) Pit.



Aortic Press.
103 mm Hg

Respirations
Cat, male
Wt - 2500
Ch. Hy - 59m
2:11:21

Signal.

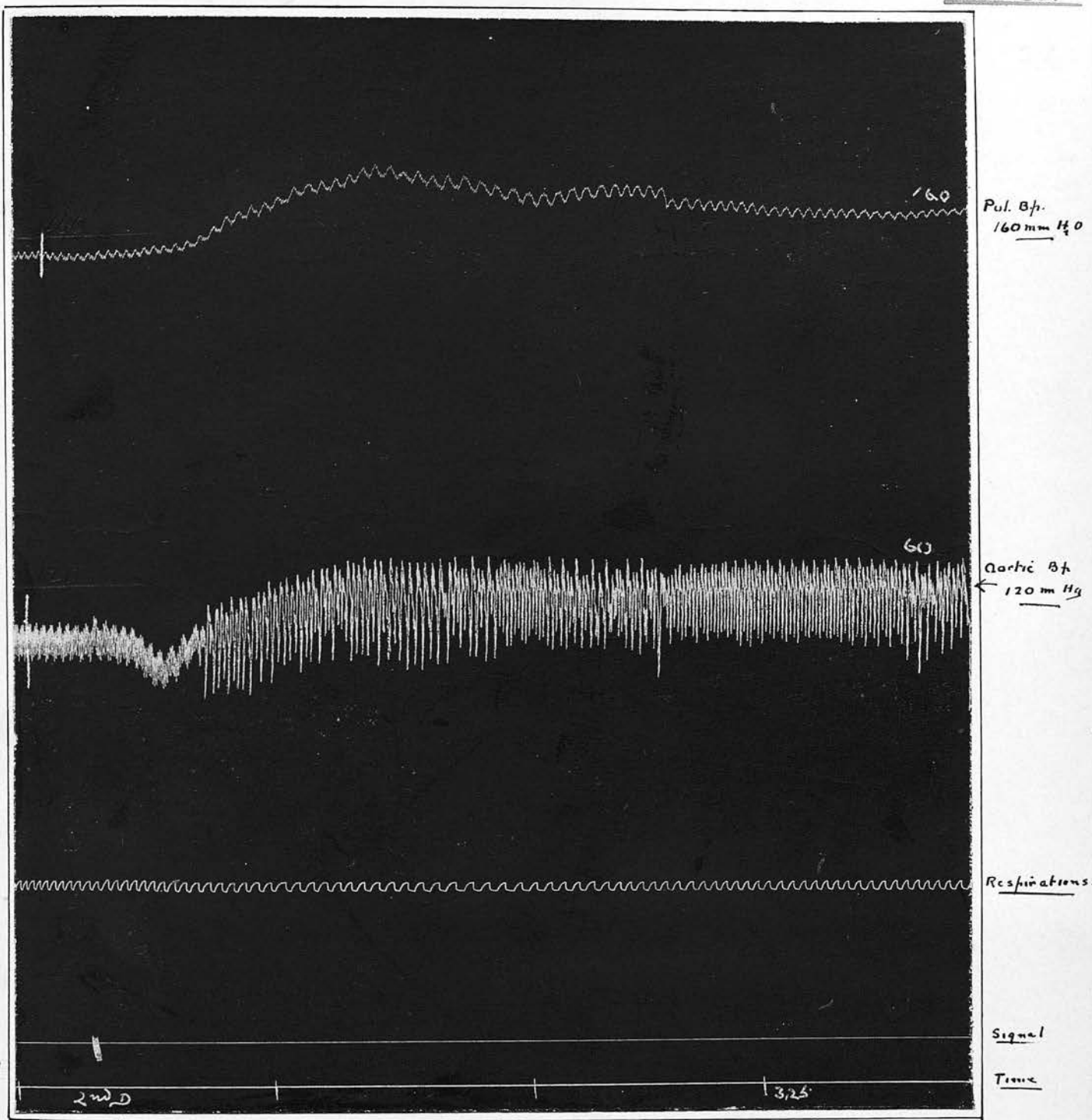
Time

Fig. 22

A ↑ Effect of first dose - ↑ Arterial injection

Note - Rise in both pulmonary and aortic pressures, beginning in aortic
Some cardiac and respiratory irregularity in "A".

↑ = Simultaneous points



Cat, male
Wt. 2500 gm
Ch. Hgt. 5.9 cm
2:11:20

↑
Simultaneous points.

ICC. Pit. (Martindale) 2nd Dose into Artery. (1st D. Sec Figure)

Note

Rise in pulmonary \bar{c} fall in aortic - negates the possible effect of back-pressure (cf. Fig. 24)

Rise in pulmonary begins before rise in aortic. (cf. Fig 21)

result of constriction of the systemic arterioles has however to be more seriously considered, indeed there is much evidence that it does occur, although only in a small number of cases.

In rabbits especially has this effect been noted and it will be remembered that in the perfusion experiments the fact that these animals occasionally show a very accentuated constrictor effect was remarked upon.

An instance of this is well shown in fig. 25. It will be seen that the pulmonary had begun to rise as the result of the intravenous injection, but as soon as the injection reached the systemic side and the aortic pressure began to rise, the rise in the pulmonary was converted into a fall. Subsequently this state of affairs was reversed as will be discussed later. In figure 25 the influence of the respiration must be considered as it will be noted that the respiration became somewhat inspiratory. This may have been an additional factor in determining the commencement of the effect, but as a similar short inspiratory phase occurred a little later which was not accompanied by similar pressure changes, it cannot be considered to have been the real cause.

Fig. 26 shows another instance in which an inspiratory phase or a deficient expiration determined a similar fall in the pulmonary blood pressure. ~~See diagram.~~

EFFECT OF

FORWARD ACTION

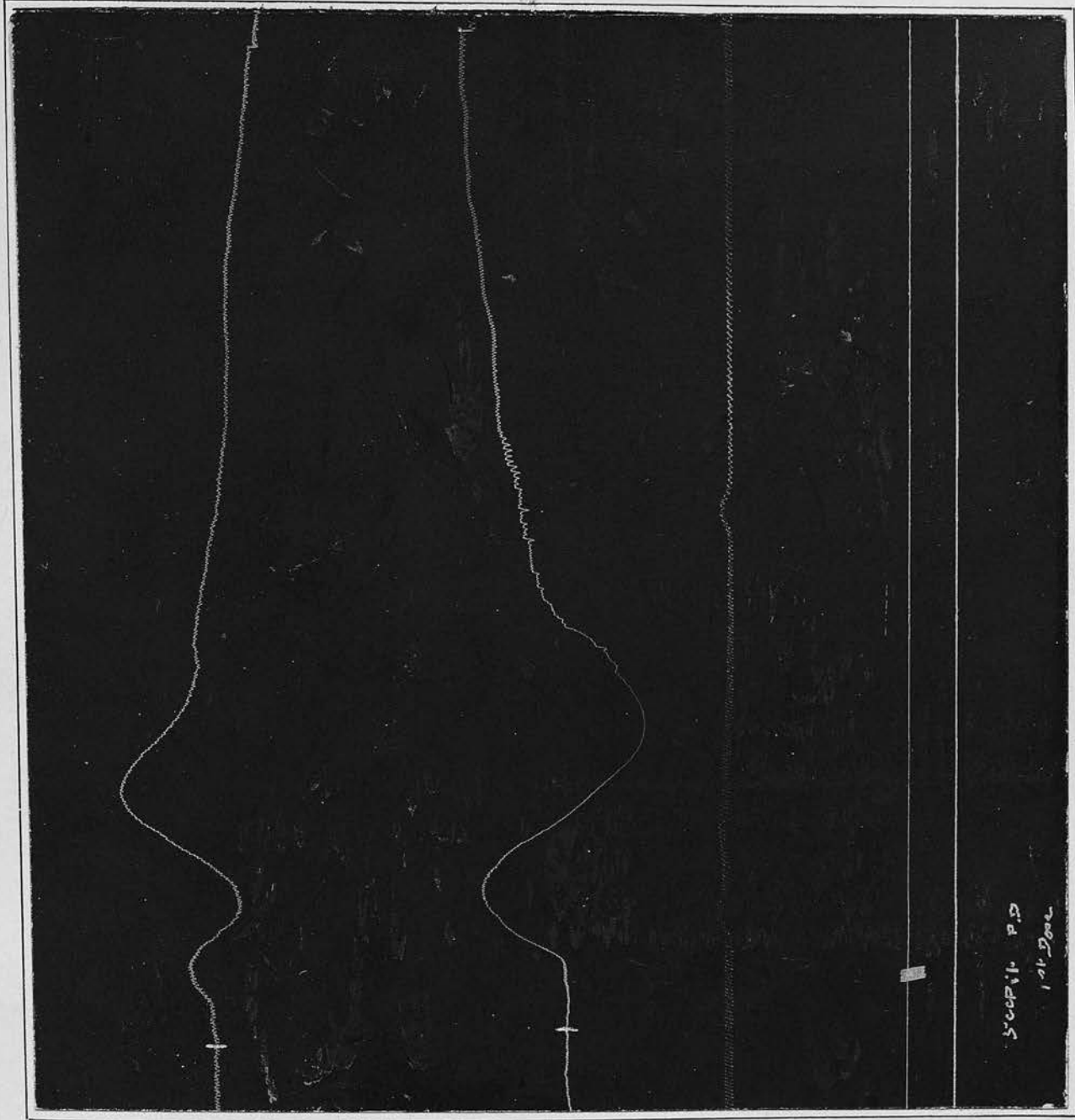
Note

Initial rise in pulmonary converted into a fall by rise in aortic. Subsequent fall in aortic on rise in pulmonary. Also inspiratory phase "A" which was probably contributory although not in itself sufficient to cause the pulmonary fall as seen in "B".

↑ = simultaneous points.

Rabbit, male.
wt 1900 gm.
ChHyp .5 gr.

14:9:20



5000 P.D.
1st Dose

↑ A 0.5cc Pituitrin. (P.D.9 Co) 1st Dose. in 16. Dose

The 2nd & 3rd doses gave a slight rise in each but no evidence of forward action.

Pulmonary Press.

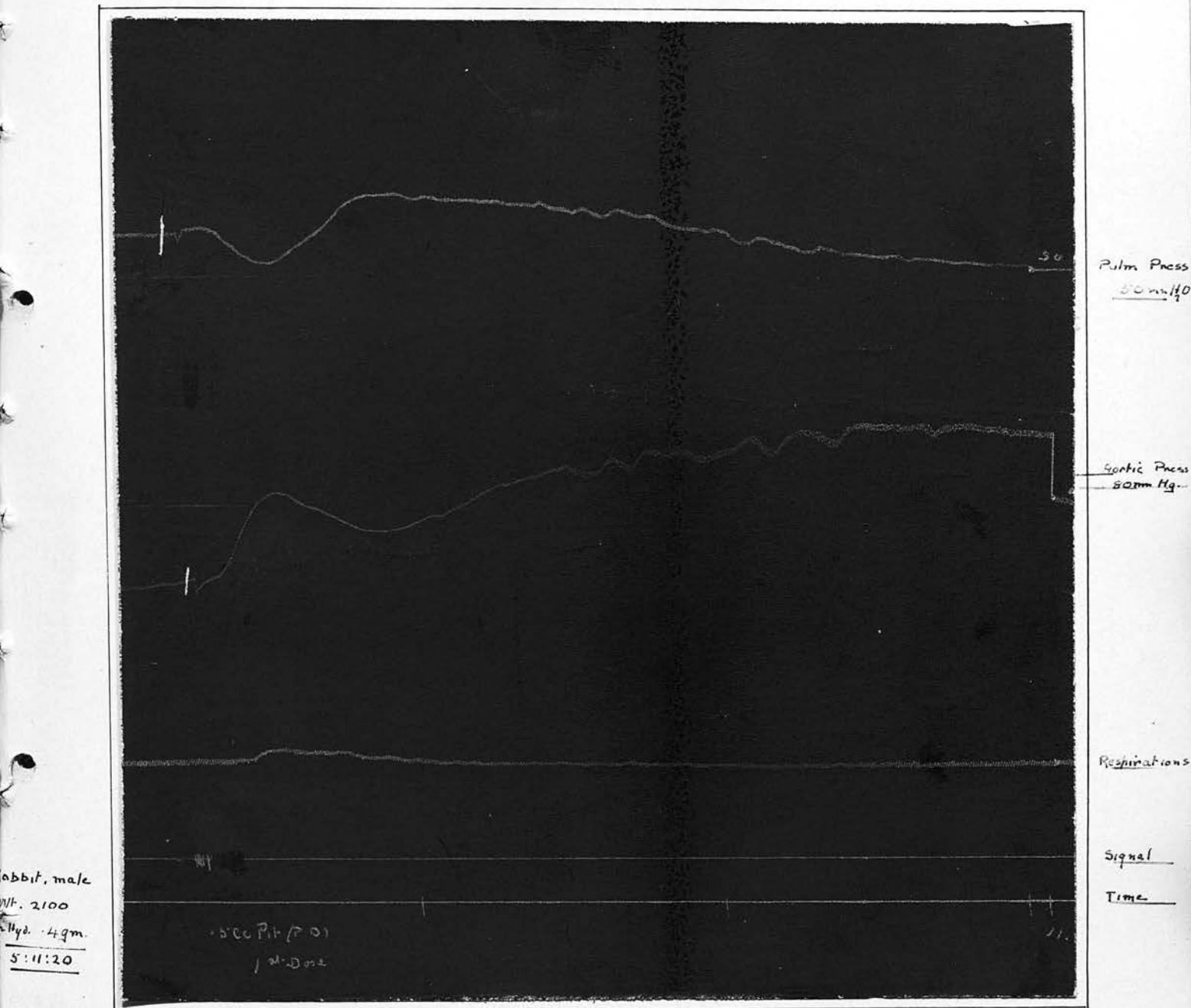
Aortic Press.

Respirations.

Signal.

Time.

719.25



5cc Pituitrin. (P.D. & Co) 1st Dose into vein

Note EFFECT OF "FORWARD" ACTION

Initial rise in pulmonary converted into fall by rise in aortic and inspiratory phase. Subsequent dip in aortic due to rise in pulmonary. (cf. fig 25)

Waves seen in later part of tracing due to spontaneous movements in blood-vessels.

(see similar tracings in part 3 of this paper.)

On the other hand in the majority of cases the pulmonary fall occurs most frequently when there is little or no rise in the aortic (i.e. 2nd or subsequent doses) indeed there may be a marked fall ^{or no change} in the aortic. Figs. 18 and 19).

That the changes in the pulmonary system are not due to changes in the capacity of the whole vascular area is seen by the differences between the two circulations and the different effects of 2nd or subsequent doses in the same animal.

It may therefore be concluded that the changes which occur in the pulmonary circulation are due to the effect of the pituitary extracts upon the pulmonary vessels, except in case of some rabbits where some effect may be due to changes in the aortic through "forward" action.

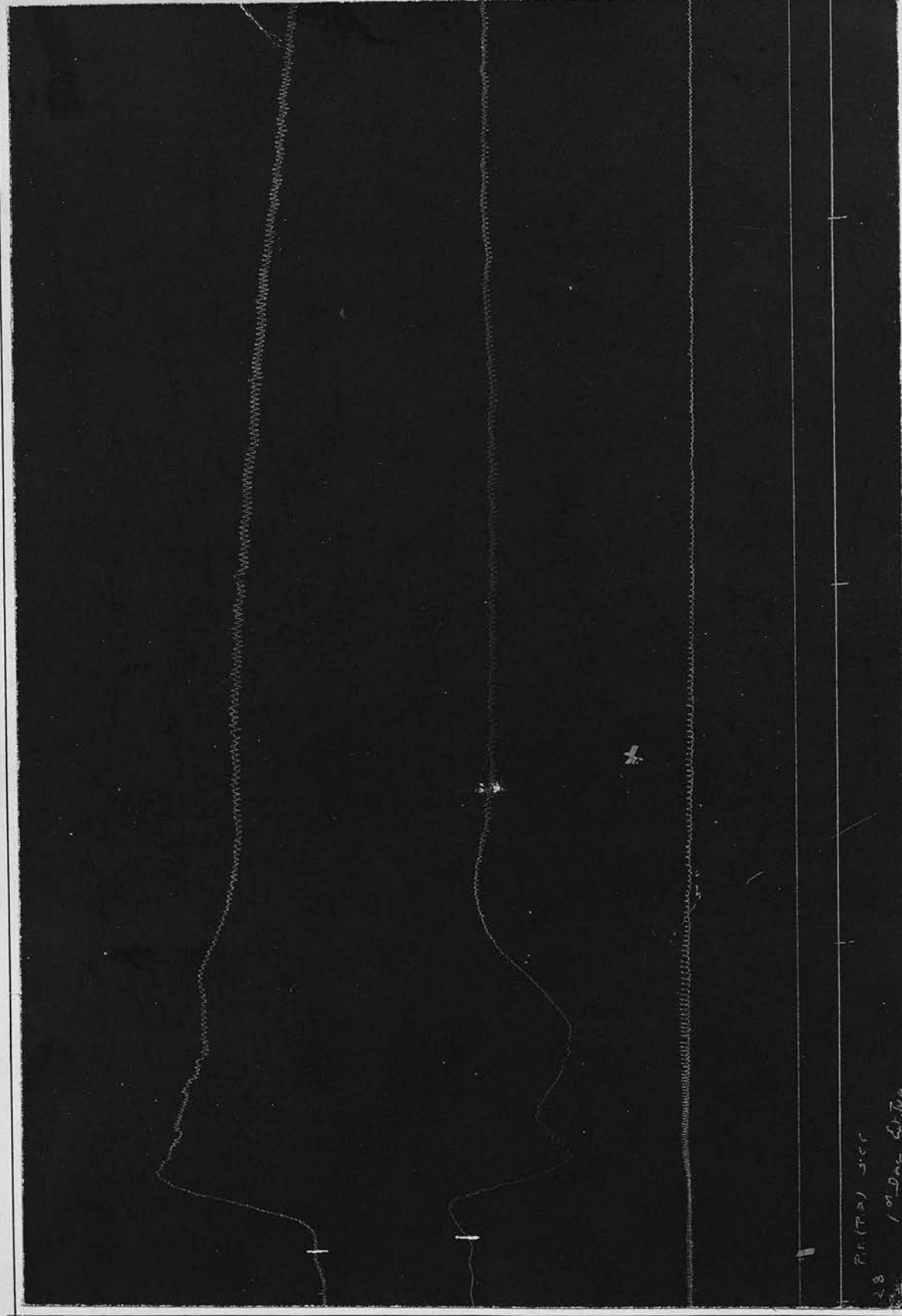
What, then, it may be asked, is the effect of these pulmonary variations upon the aortic circulation, for it will be noticed that many of the rises in the pulmonary circulation are approximately coincident with falls in the aortic, and particularly is the fall - which is so difficult to account for - in/

in the aortic pressure which is found after the 2nd or subsequent doses of pituitary, due to the influence of the pulmonary circulation.

Back Action. This is at once dismissed by the fact that in arterial injection on the first dose the rise begins in the aortic system before the pulmonary. (Fig. 22). Such back action would also involve inadequacy of the right ventricle, the semilunar and tricuspid valves. Also when the disproportion in the pressures of the two circulations is considered such "back" action is not to be expected.

Forward Action. That this does occur to a greater or less degree appears certain: Especially in rabbits, tracings in which the pulmonary and aortic curves are exactly the opposite of each other ~~they~~ frequently occur: while with intravenous injection marked instances have occurred. Figs. 20 and 27 show one of these. In it, it will be seen that the enormous and immediate rise in the pulmonary causes a fall in the aortic which has just begun to rise as is usual with the first dose. Gradually, however, the pituitrin affected the systemic arterioles and a slight constriction took place. In subsequent doses ^(Fig. 20) however the/

Rabbit, female
lot 2600
Ch Hyd .5 qu-
10-9-20.



Pit (P.D) .5 cc
1st Dose into Vein

↑
Simult. Points

.5 cc Pit. (P.D) 1st Dose into Vein

Note - Marked "forward" action. Initial rise in aortic converted into a fall by the cutting off of the blood to the left heart.

the pulmonary effect was less and the constriction of the aortic circulation is better seen.

It has been stated above that pulmonary and aortic curves which are exactly the opposite of each other are found. Fig. 28A shows one of these.

It will be noted that the rise in the pulmonary coincides exactly with the fall in the aortic and the returns of each to normal coincide.

At first sight it would appear that this was undoubtedly an instance of "forward" action, i.e. the effect of less blood passing to the left heart from the lungs. This however is only partially true, as figure 28B from the same animal shows that where the dose was increased the rise in pulmonary pressure was almost doubled, while fall in the aortic is actually less.

It is seen, therefore, that although such "forward" action may be a contributory factor in causing a fall in the aortic pressure, it is not the essential cause of the fall. This is further confirmed by the fact that the rise in the pulmonary may be of quite long duration and may be much less abrupt than the fall in the aortic. Further in arterial injections it is often clearly evident that/

that the fall in the aortic occurs before the rise in the pulmonary.

"Forward" action it may be concluded therefore only plays a small part in the production of falls in aortic pressure.

On looking through the tracings generally, however, it will be noted that the higher the pulmonary the lower the aortic and vice versa, which indicates that there is a balance between the two circulations which it may be said is a comparatively slowly acting one.

Summary. There is therefore a general agreement between the results of the perfusion experiments and those in living animals, and it is possible to arrive at the following conclusions in regard to the action of pituitary extracts on the pulmonary circulation.

The first dose causes a well marked ^{constriction and consequent} rise of pulmonary blood pressure which in a few instances may be of short duration and followed by a dilatation ^{and fall}.

Subsequent doses usually cause a constriction followed by a dilatation in perfusion experiments. In the living animal, however, there is greater variety but the occurrence of a similar result is frequent, although it may not appear till the 4th or 5th dose. Instances occur in which there is constriction only and in many there is no definite results at all.

After several injections the effect of the extract ceases to be apparent, and a few animals are insensitive from the first, especially those in poor condition.

There is no constant difference between cats and rabbit nor between venous or arterial injection.

There is evidence to show that the action of pituitary extracts is related to the nature of the solutions/

solutions with which the extracts are made. This is best seen in the perfusion experiments and the effects of the blood on this factor probably accounts for the diversity of results obtained with the second and subsequent doses in the living animal.

In rabbits especially, in which large rises of pressure with pituitary extracts not infrequently occur, the effect of "forward" action may be well seen. It is usually the effect of a constriction in one circulation in preventing access of blood to the other and a consequent fall of pressure in the ~~other~~ other.

Within wide limits, however, the pulmonary and systemic circulations are independent of each other and one is not affected by rapid changes in the other, although generally the higher the aortic pressure the lower the pulmonary, and vice versa.

Observations on the Research.

By this research considerable light is thrown on the dynamics of the pulmonary circulation. Until quite recently it has been generally assumed that the pressure of the pulmonary circulation was largely dependent on that of the systemic. Since the introduction by Sharpey Schafer of more accurate methods of investigating the lesser circulation considerable evidence has accumulated which goes to show that within wide limits the circulations are independent of each other. Further weight is therefore added to this evidence, particularly in regard to the dilatation of the pulmonary vessels which hitherto has not been shown to be effected by drugs. Furthermore it is seen that a mechanism exists for constriction and dilatation of the pulmonary circulation - a fact which has been much denied. Confirmation is therefore given to the work of Sharpey Schafer who found that a lowering of the pulmonary blood pressure could be effected independently of the aortic change by stimulation of the central end of the depressor nerve, also to the work of Bradford and Dean, who got constriction by/

by stimulation of the upper thoracic nerves. The work of Brodie and Dixon which has already been referred to as being experimentally fallacious in respect to the pulmonary circulation, and which has played the largest part ⁱⁿ negating the existence of vasomotor control in the lungs, is contradicted.

Another interesting feature is the evidence that pituitary extracts cause a rise followed by a fall in the pulmonary circulation which is the opposite of what frequently occurs in the systemic circulation, namely, a fall followed by a rise. In the light of our present knowledge of the chemistry of the pituitary - practically nil - this fact is all the more difficult to understand.

It has already been suggested by Brodie and Dixon, as the result of their negative experiments with adrenalin and the stimulation of nerves that only the larger arteries have a sympathetic nerve supply. This view is supported by Dale, to explain the difference between the action he obtained with pituitary extract and the results of Brodie and Dixon: while Cow uses the same suggestion to explain the fact that with adrenalin he could get constriction only with the larger vessels, a fact explained by Schafer and Lim to be due to the fact that the smaller/

smaller rings were not powerful enough to raise the lever. As this hypothesis is founded on the work of Brodie and Dixon which has not been confirmed, little stress can be put on it. It could not be expected that this could be the explanation of the action of the pituitary extracts as a dilatation occurring distal to and at the same time as a constriction would not be shown by the means herein adopted, but it is conceivable that a short-lived contraction of the larger arteries might be followed by a dilatation of the arterioles. It is however difficult to reconcile this hypothesis with the more sustained contractions which occur, and with the fact that the opposite occurs in the aortic system.

That there is some balance between the two circulations is suggested by the facts that the higher the pulmonary the lower the aortic and vice-versa, and by the fact pointed out by Sharpey Schafer that the less the effect of stimulation of the depressor nerve on the aortic pressure, the more on the pulmonary.

It is also to be remembered that in the pulmonary circulation ^{blood} passes from the venous to the arterial side while in the systemic the opposite is the case.

If tracings of 2nd or subsequent arterial injections be investigated it will be noted that in these, /

Pul. press - 160 mm Hg.

Arterial press. 100 mm Hg.

Note

1st D → rise.

2nd D → No change

3rd D → little change

4th D → rise & fall

5th D → " "

6th D → " "

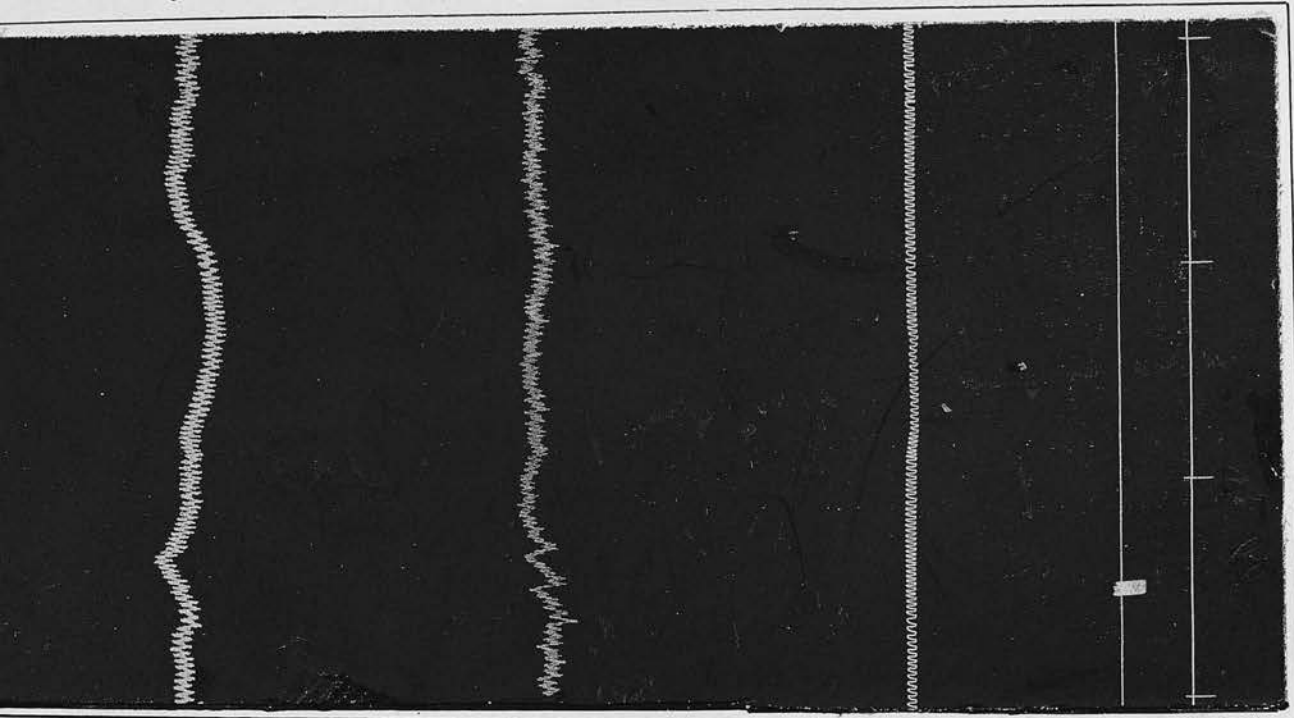
Note that the rise

and fall became

marked after 4th Dose

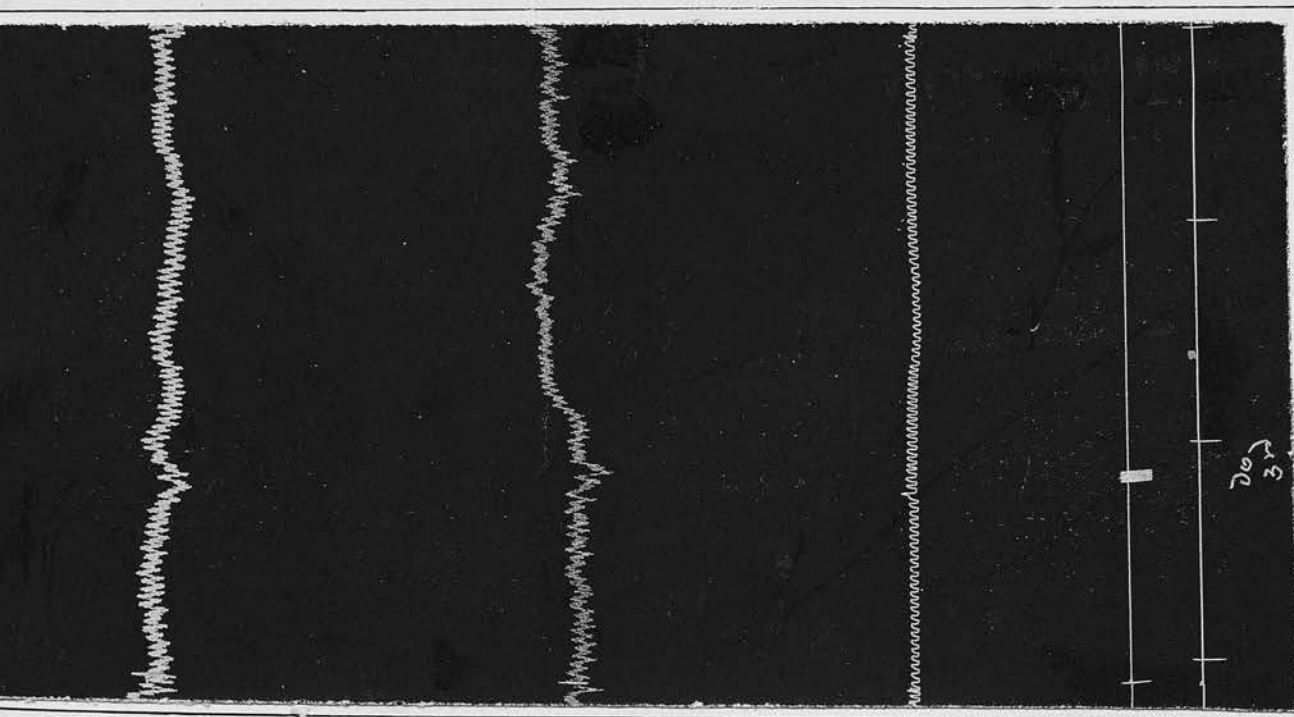
28

Fig. 19c



ditto. 4th D

Definite rise & fall in pulmonary



↑ 1cc Pit. Ext. 2 1/2% in 10 min 3rd Dose

Little change in pul.

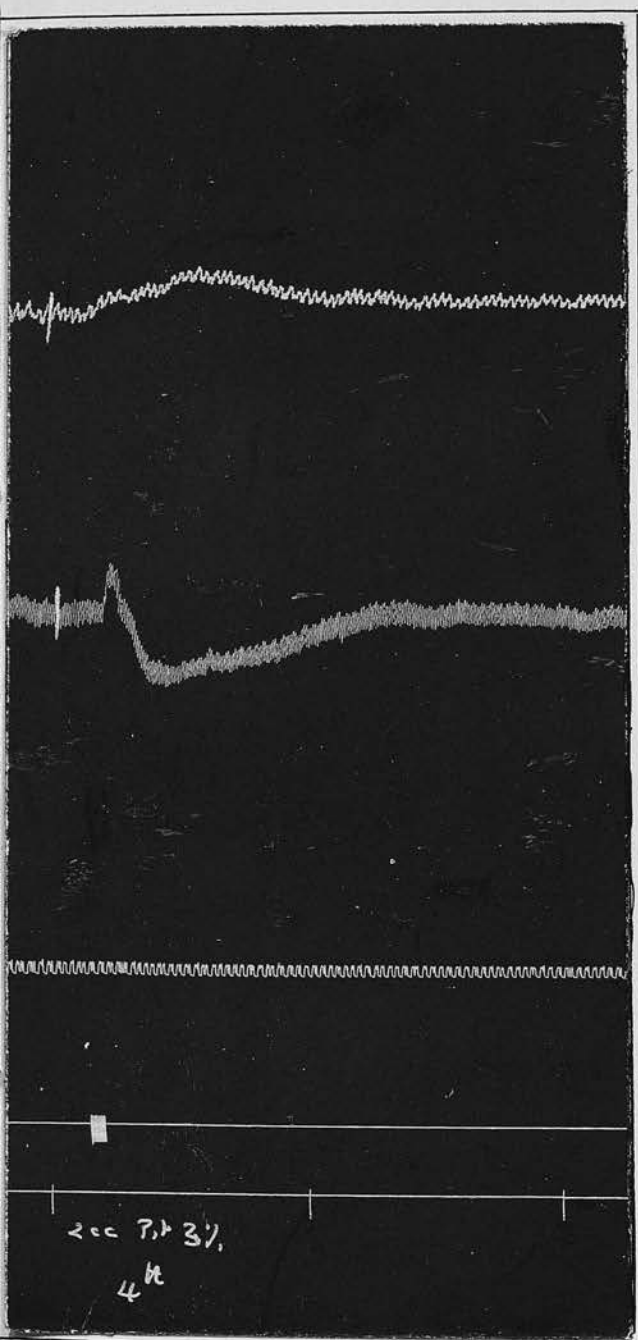
Similar to Figure 19

Cat, male.

Wt. - 2650 gms

ELL - 5'9m.

15-1-21



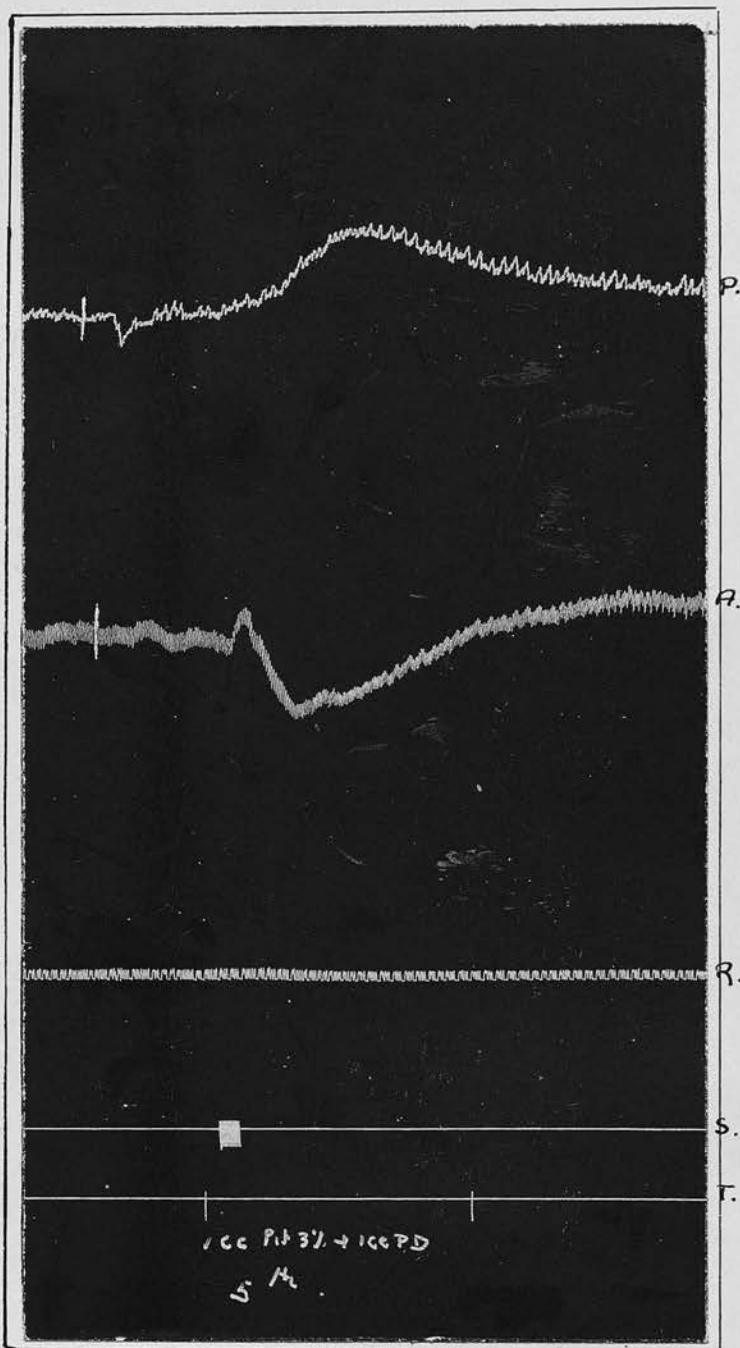
↑ 2cc Pit. Ext. 3% 4H D

Cat, female (preg)

wt. 2000 gm

19-2-21

↑ = Simultaneous points.



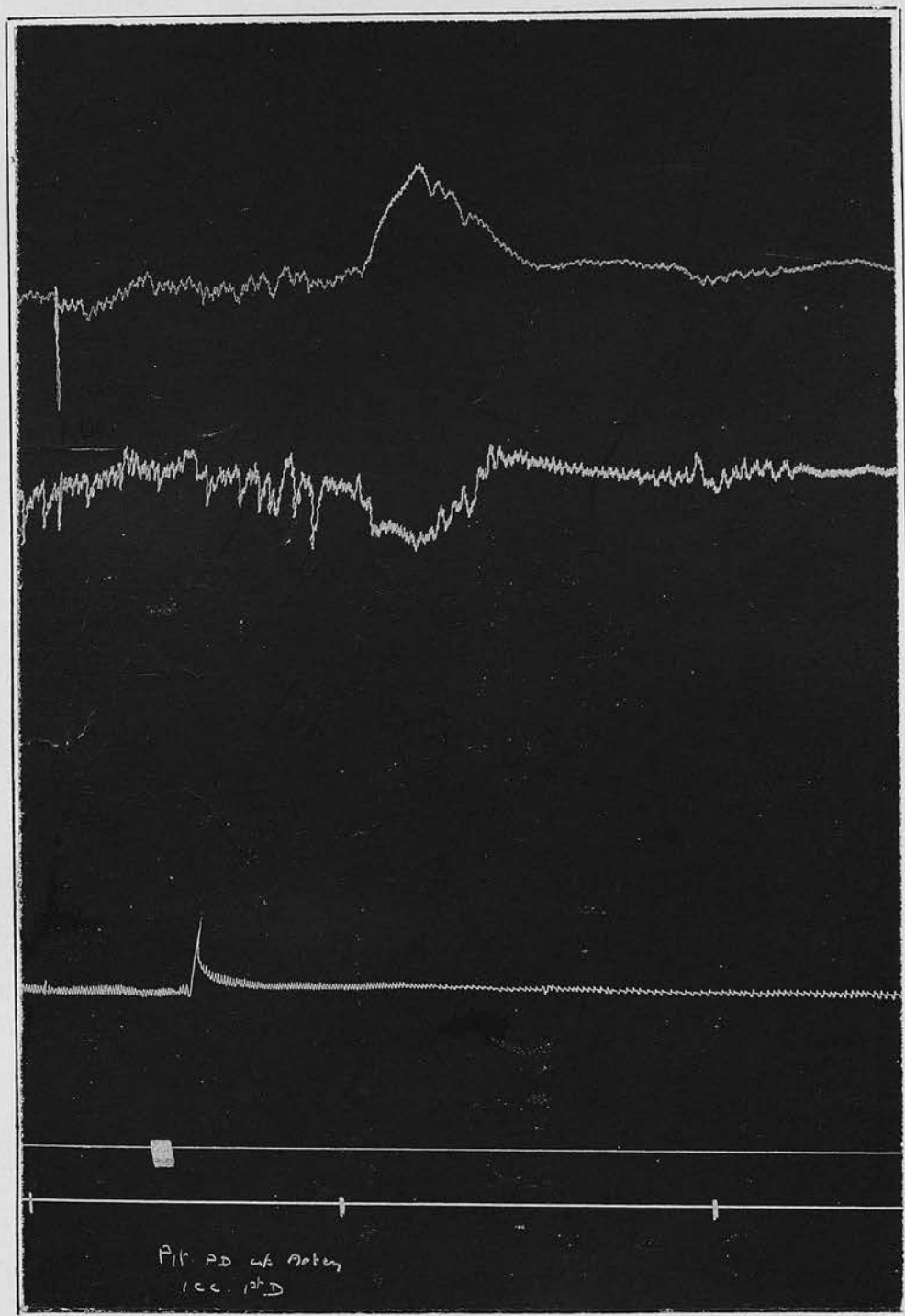
B ↑

1cc Pit. Ext. 3% + 1cc Pit. (P.D)

Both. int. artery

Note - Although the dose has been increased, there is little difference in the aortic falls. There is however a marked increase in the pulmonary rise. It must be noted that the initial aortic pressure is lower in "B" than in "A"

Fig. 28B

Pulmonary blood-pres.Aortic blood-pres.Respirations.SignalTime.

Cat, female.
Wt. 2800 gms.
Hyd.

Pit. AD into Artery
1cc. 1st D

1cc. Pituitrin (P.D. & Co.) 1st Dose into Artery

Note Presumably the constrictor factor of the pulmonary has passed through the systemic arterioles causing them to dilate. The respiratory irregularity being inspiratory would have caused a fall in the pulmonary y any change. (c.f. Figs 25 and 26)

these, constriction begins in the pulmonary long before the systemic, although the extract passed through the arterioles of the latter first, indeed in it is seen that in some instances the rise in the pulmonary pressure almost coincides with the fall in the aortic (Figs. 19, 28A and 28B).

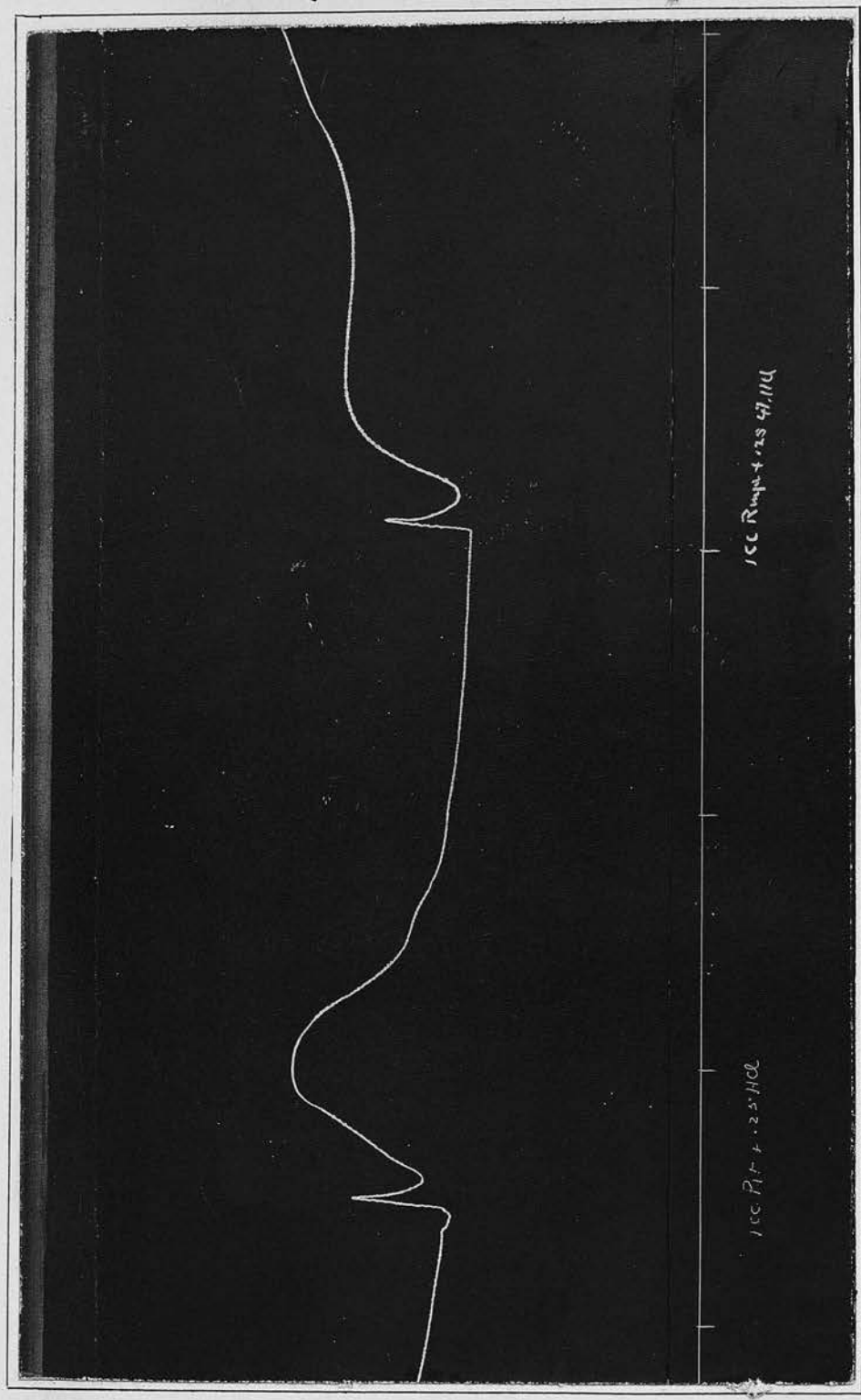
When however there is no preliminary dilatation of the systemic as is usually found with the first injection, the constriction begins in the systemic as would be expected. (Figs. 22A and 22B).

This would go to show either that the depressor factor for the systemic circulation is responsible for the constriction in the pulmonary and vice versa, or that the pressor agent passes through the systemic circulation without affecting it as a result of a more powerful action of the depressor factor.

Were the latter possibly the case with intravenous injection, the depression would be expected to occur in the pulmonary circulation also before the constriction. This, however, is not the case.

The evidence is therefore in favour of the hypothesis that the factor which constricts the pulmonary is that which dilates the systemic. Further, in the second part of this paper (Figs. 12 & 36) it/

Cat, female.
 Wt. 3000
 3-3-21



Manometer record
 only

Time in minutes

1 cc Pituitin (P.O.) + .25 cc 4% HCl.

1 cc Ringer + .25 cc 4% HCl.

Perfusion of hind limbs. \pm Ringer Locke Solution.

Note — The effect of Pituitrin in counteracting the effect of HCl. A previous injection of HCl. was given with the similar result of prolonged constriction only. The result proceeded to occlusion.

Jan 29.

it will be noted that the production of waves by pituitrin occurs during the dilatation, showing that whatever the actual cause of the dilatation there is also a stimulating action possible.

Further it is to be remembered that in the perfusion experiments neutral solutions gave constriction only, while alkaline solutions gave dilatation, and that Argyle Campbell obtained a similar effect. The acid pituitrins such as that of P.D. & Co. also caused a dilatation. Figure 29 shows a clear instance of similar action in the systemic circulation. In it is seen the antagonistic action of a pituitrin (itself acid) on an injection of .4% HCl which alone caused a powerful constriction.

Also it has been shown by Severini and Gaskell that the calibre of blood vessels is markedly affected by the reaction of the tissues through which they pass. They found blood vessels constrict in the presence of oxygen and dilate with carbon dioxide, which latter fact has been confirmed. (Cow, ^{Roy, Graham Brown etc.} ~~and another~~).

The above is a summary of extremely interesting facts and it is difficult to avoid thinking that the whole action of pituitrin is bound up in them. The sensitiveness of arteries to minute changes in hydrogen/

hydrogen ion and the similar sensitiveness of pituitrin to like changes appear to be associated with each other, and when it is considered that an essential difference between the arteriole and capillary areas of the two circulations is the degree of hydrogen ion concentration of the fluids with which these areas are bathed, a solution to the difference of the two circulations in their action to pituitary extracts appears not far distant.

The actual formulation of a hypothesis, however, must await the result of further work and could more suitably be included in a paper on the action of the pituitary than in one on the physiology of the pulmonary circulation.

P A R T 3.ON SPONTANEOUS MOVEMENTS IN BLOOD VESSELS
WITH SPECIAL REFERENCE TO THE PULMONARY CIRCULATION.

The occurrence of rhythmical fluctuations in the systemic arterial blood pressure is well known, and it has been generally assumed that they are the result of overflow of impulses from the respiratory to the vasomotor centre consequent on asphyxial or anaemic conditions of the bulbar centres. Many observers have noted the existence of rhythmical movement in individual arteries. It has been described by Wartan, Jones, Reigel, Savoille and by Gunning, in the vessels of the bat, in the mesenteric, peritoneal and web arteries of the frog and in mammals it has been observed in the saphenous artery of the rabbit which is stated to contract once or twice a minute, but more frequently it has been noted in the vessels of the ear of a rabbit.

In 1875 Mosso with his plethysmograph showed that the human arm exhibited irregular oscillations which he interpreted as the effect of a peculiar rhythm of alternate contraction and dilatation of the/
the/

the vessels of the limb. This was subsequently confirmed by Von Basch with a weighing plethysmograph. Mosso also described a constant irregular oscillation in the isolated dog's kidney placed in a plethysmograph and artificially perfused. This he considered to be dependent on oscillations of tone in the renal vessels. It was certainly not dependent on the central nervous system, although the possibility of the activity of peripheral ganglia is not excluded.

In connection with the rhythm seen in rabbit's ear it was noted by Foster that if the animal be held up by the ears for a few minutes the movement was better seen, a fact which suggests the effect of a local stimulus of a stretching nature.

In 1902 Bayliss found that the muscular coat of an artery reacted like smooth muscle in that, on being stretched it responded by contraction. It also reacted to a diminished tension by relaxation which is shown only when the vessel is in a state of tone. These reactions were shown to be quite independent of the central nervous system as they could be obtained not only from vessels in their normal state, but even in excised arteries. He states if an excised artery be tied at one end and the/

the other be connected by means of a cannula to a head of fluid the pressure of which could be varied, that on varying the pressure the artery writhed like a worm. Bayliss concludes that the contraction is purely of myogenic origin. At an earlier date, Poisselle["] (confirming the work of J. Hunter) found that an artery dilated by injecting a fluid reacted with a force superior to the impulse of the injection. By comparison of a fresh artery with one excised several days before - in which only the elastic element remained, - he confirmed his contention that the contraction was due to the action of the muscular coat.

More recently, spontaneous contractions of vessels have been investigated by Kravkov. He finds that they are best seen in the arteries of the isolated gills of fishes, but he notes their occurrence in isolated arteries of the ear and brain of the rabbit, and also in the coronary vessels of the heart stopped by strophanthin. He found that they were unaffected by nervous elements as nervous poisons do not affect them.

The existence of a similar rhythm has also been observed in rings or spirals of arteries. Sherrington in his "Mammalian Physiology" states that in a surviving/

surviving spiral of artery made to activate a lever "probably no beats will be seen". The accompanying illustration however is a tracing by Denniston which shows beats which have evidently been excited by the action of adrenalin. This stimulative action by adrenalin is also noted by Schafer and Lim in their paper on the effect of that autocoid on the pulmonary circulation. Special attention was paid to it by Cow who found the same action of adrenalin on rings of arteries. He notes that the rhythmical contractions induced by it are at the rate of one in twenty-five seconds and he asks himself the question. Are these Traube-Hering waves? There unfortunately he leaves the matter.

De Bouis and Suzanna found with rings of the pulmonary artery that after pituitrin waves were produced which lasted for two and a half hours.

The spontaneous occurrence of such movement in rings of arteries has recently been described by Roucato who used very sensitive levers, like those of Vicentini's microsismograph, and made a careful investigation of the conditions affecting the contractions. He considers it essential to keep the preparation in oxygenated pericardial fluid at 38° - 39° C. He states that the movements are not obtained in artificial fluids such as Ringer or Locke's/

Locke's, and if they are artificially provoked they are of very short duration.

Roucato also remarks on the existence of slow tonic movements as well as the more rapid rhythmical ones; the tonic movements may precede the rhythmical and persist longer - for a few days even, if the preparation is kept under good conditions. He found that excessive tonic contractions or relaxations tended to interfere with the rhythmic movements which lasted generally one or two hours. The spontaneity, duration and frequency was that usually associated with unstriated muscle.

These facts bring me to the results of my own experiments which complete the evidence at least regarding the pulmonary circulation that these movements occur quite spontaneously and may be demonstrated by suitable means.

As shown in the accompanying schema the method consists essentially of introducing the pulmonary circulation into what is usually described as a piezometer system to illustrate side pressure due to resistance. The pulmonary vessels act as the stop-cock. Any variation in calibre of the pulmonary vessels is at once seen by a rise or fall in the proximal piezometer (in this case the manometer) as a result of the change in resistance. Fig.1.

The/

Fig. 30

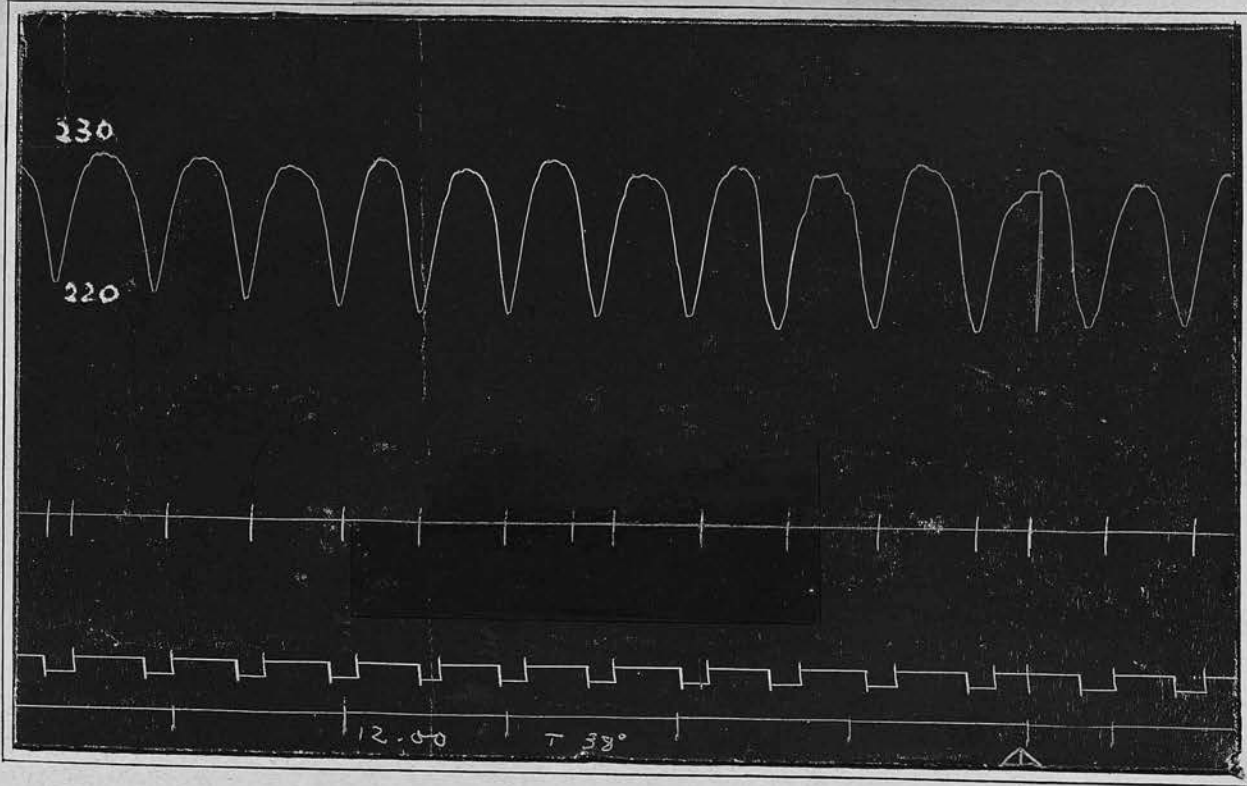
Manometer

Tiller

Signal

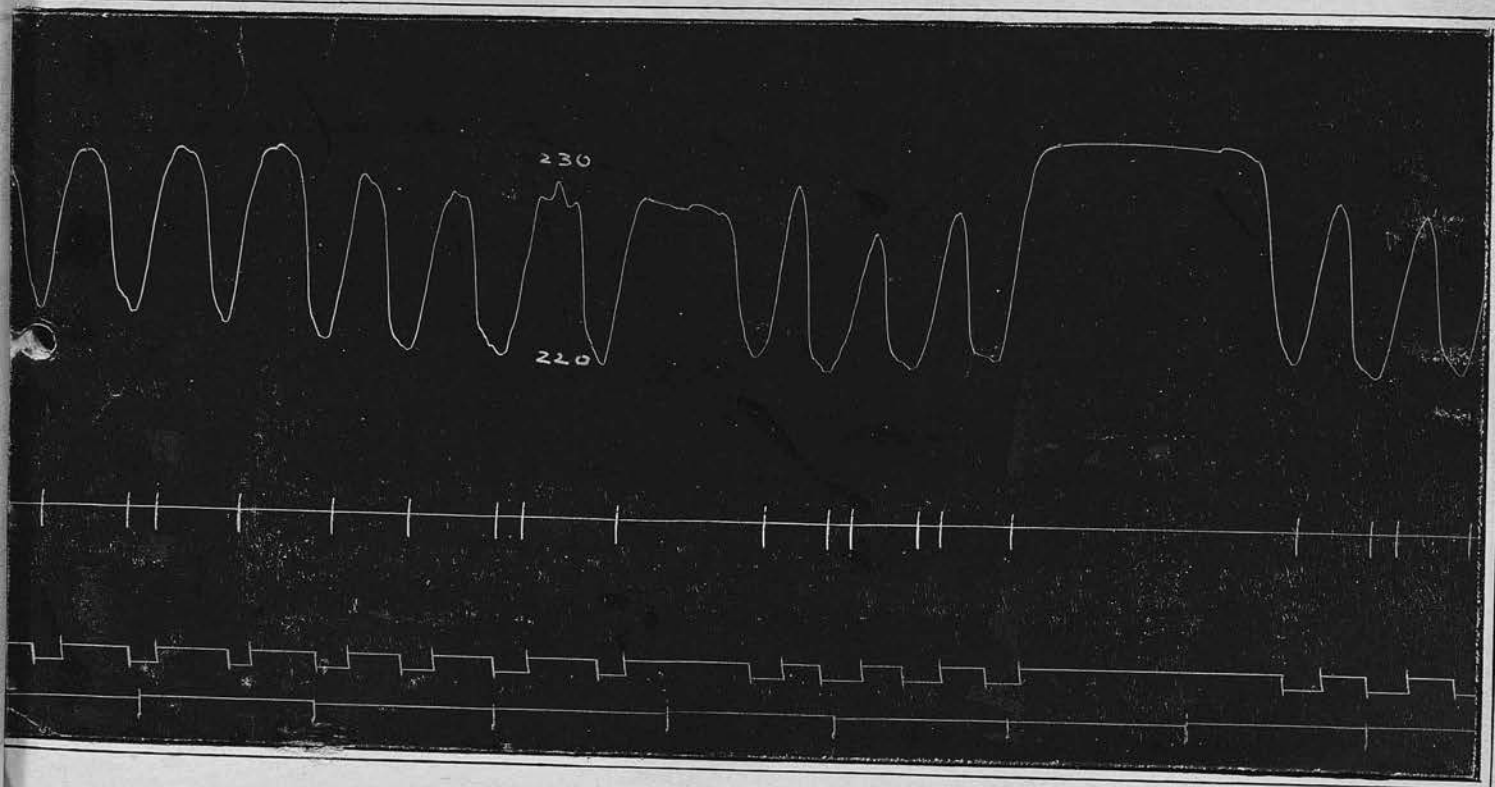
Time

essentially
given by
photographs.



Continued from 1

Simultaneous points.



Spontaneous Waves in Pulmonary Circulation in Cat.

4-2-21

Cat, female.

wt 1680 gms.

Perfusion with Ringer Locke Solution
(without Bicarbonate) at 38°C.

Signal - down = free flow from
exit tube

Cat, female,

wt 1680 gms.

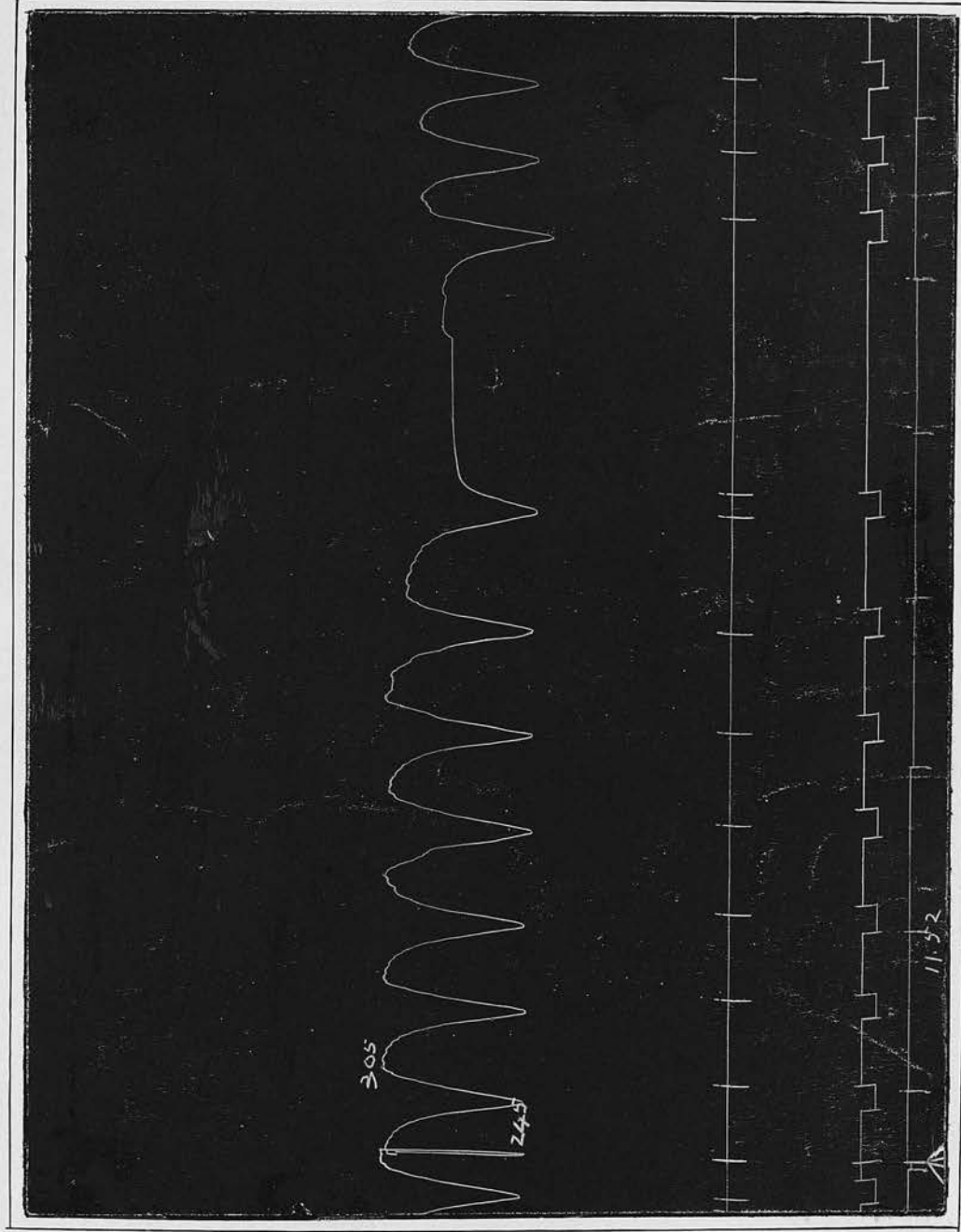
4-2-21

Manometer

Tiller

Signal

Time



↑ Simultaneous points.

Spontaneous Waves in Pulmonary Circulation of Cat

During Perfusion with Ring-Locke Fluid. (without Bicarbonate)

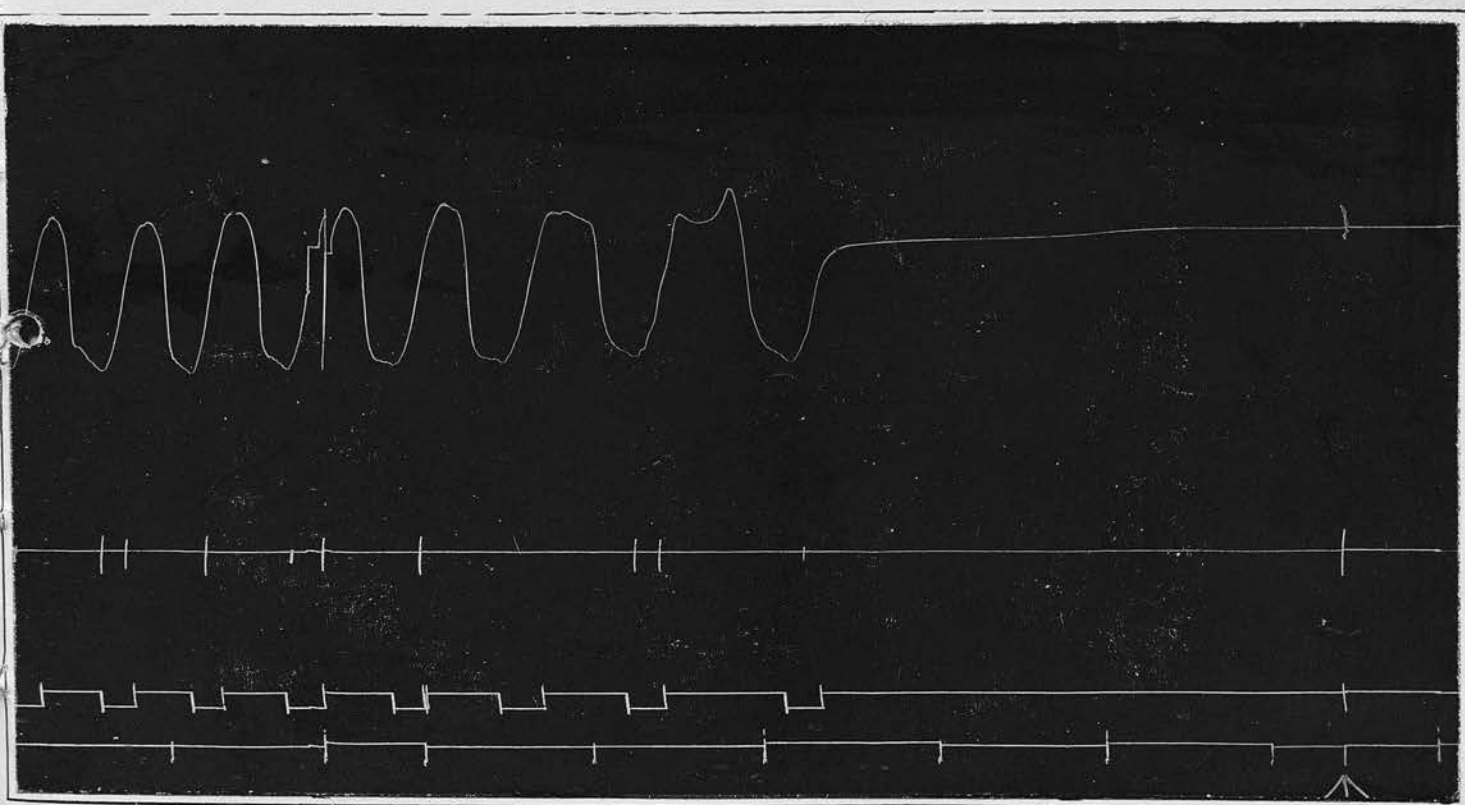
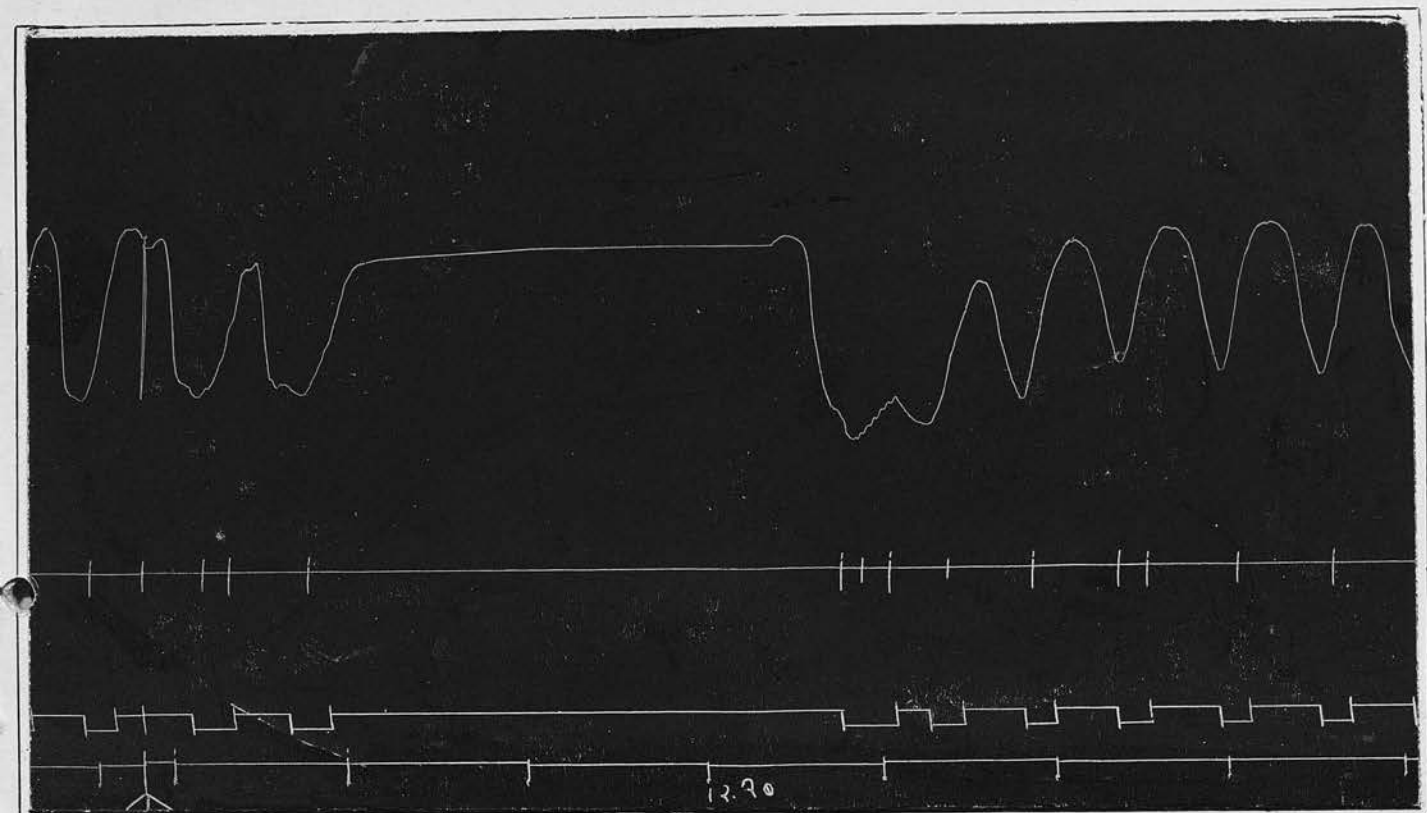
Signal-down = free flow from exit tube

Note - Free flow from outlet occurs during dilatation and just after.

Variations not shown by

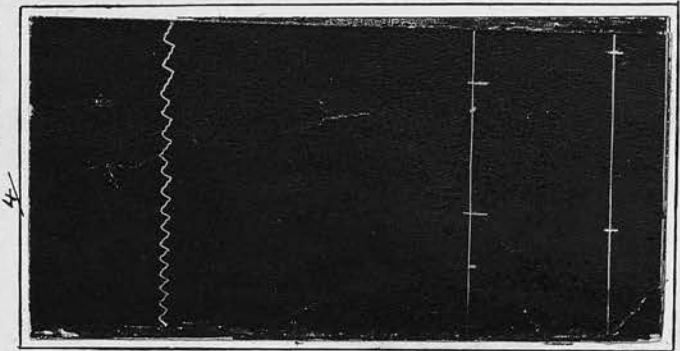
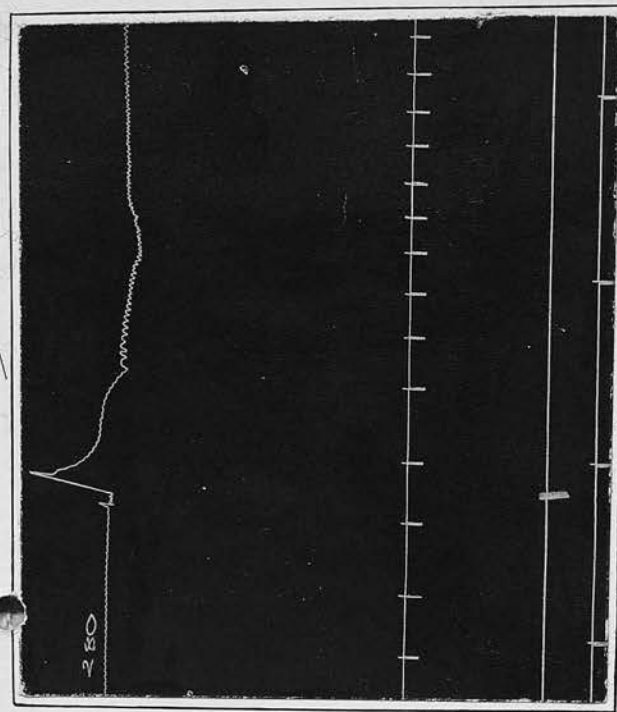
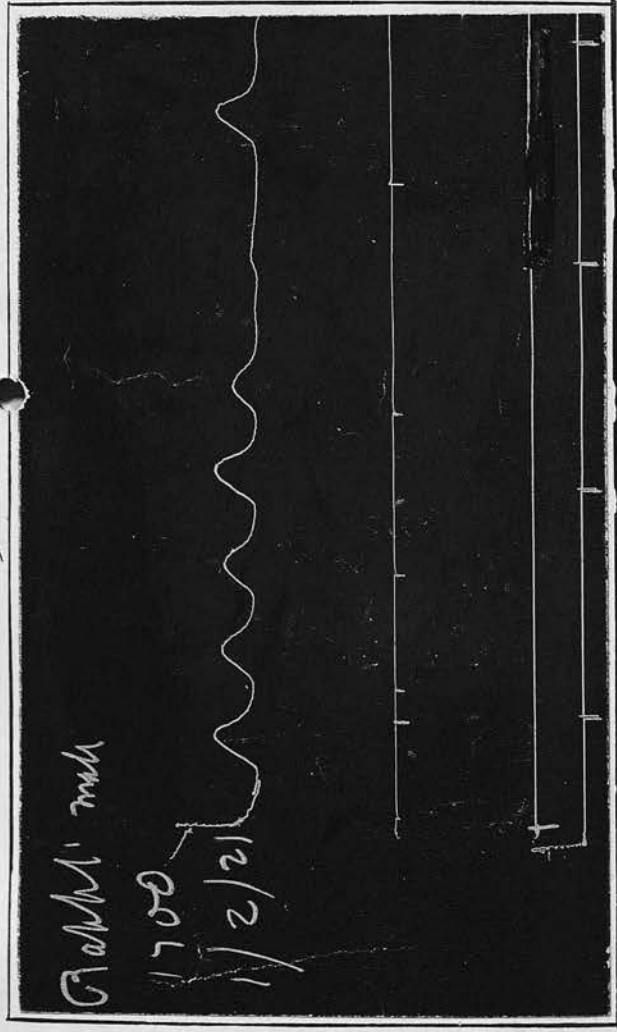
Fig.

30A.



a continuation of figure 30

↑
Simultaneous points



- 1 Spontaneous waves at beginning of experiment.
- 2 Production of waves by Pituitrin (ice P.D.)
- 3 Spontaneous waves in middle of experiment.
- 4 More rapid waves at end of experiment.

Note - Waves increase in rate. Small respiratory waves also seen.

Rabbit, male.
wt 1700 gms
Perfusion with
Ringer-Locke Fluid
± out Bicarbonate

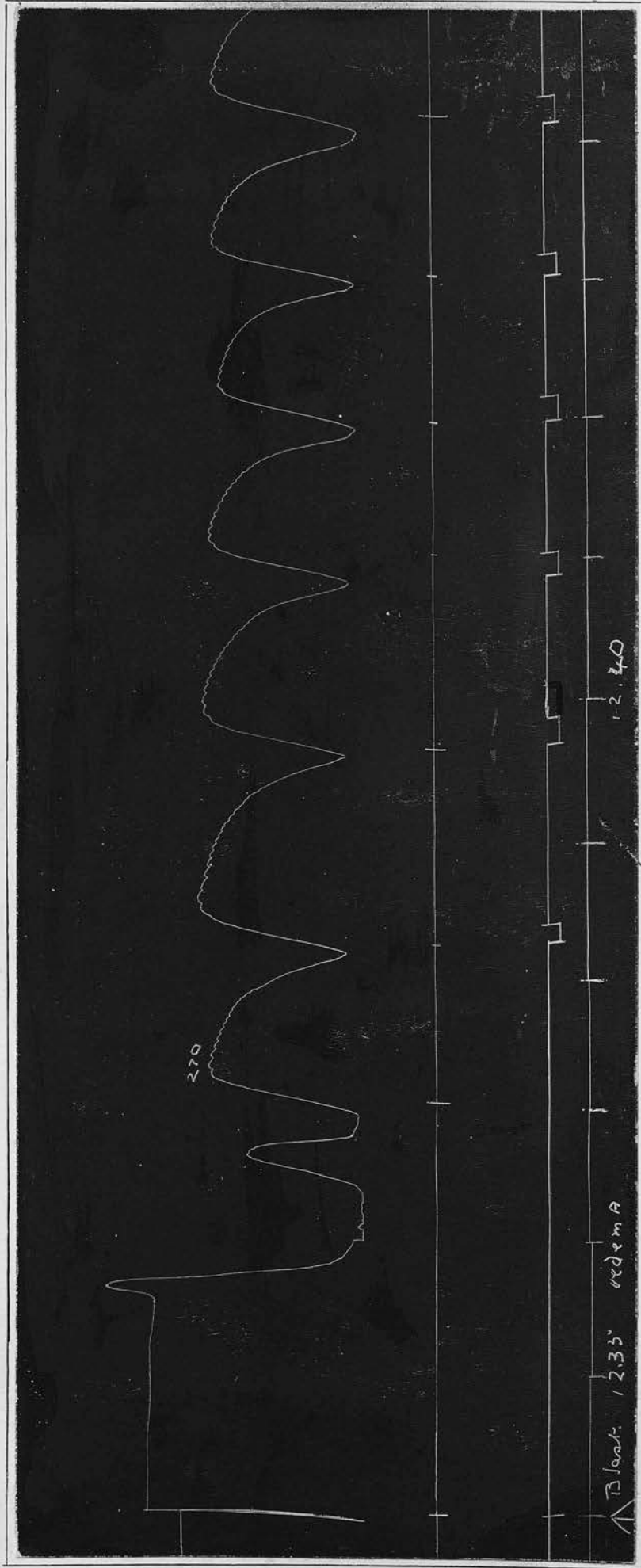
Manometer

Fitter

Time

Fig. 31.

Spontaneous Waves in Pulmonary Circulation of Rabbit



↑
Simultaneous points

Cat, female

Wt 1600 gms.

Perfusion with Ringer-Locke
without Bicarbonate.

4:22:21

Waves after edema has occurred and
after stoppage at a lower pressure.

Stimulation by distension of lung

Note Signal down = free flow
from outlet tube

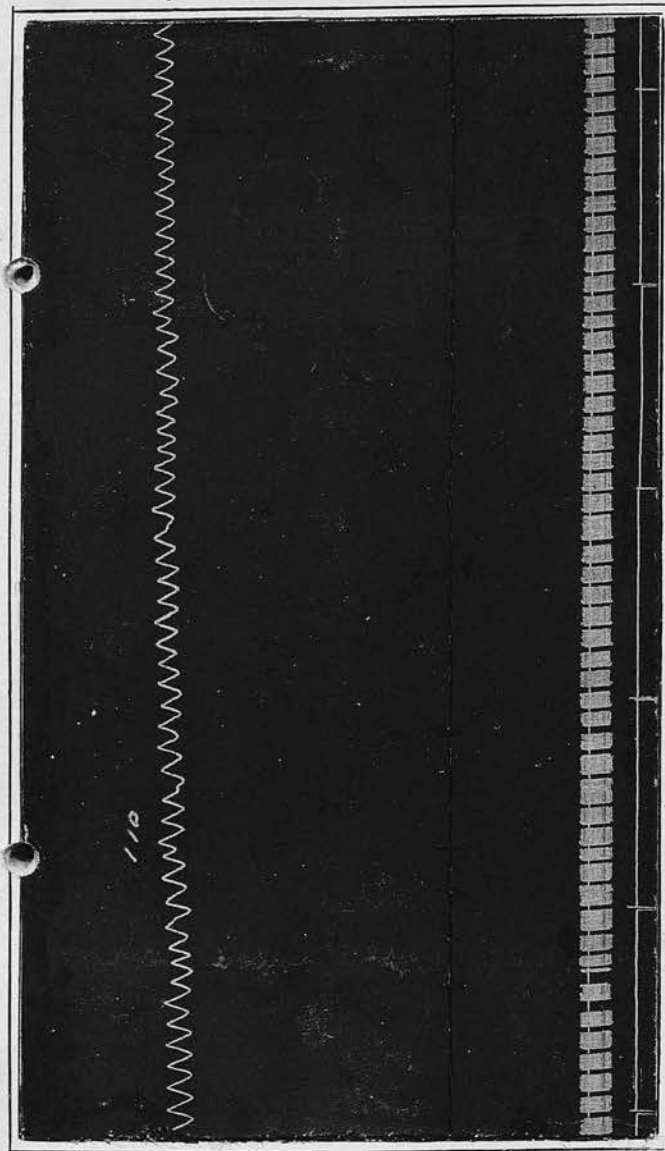
Variations - not shown by filter

Fig. 32.

Waves at
different pressures.

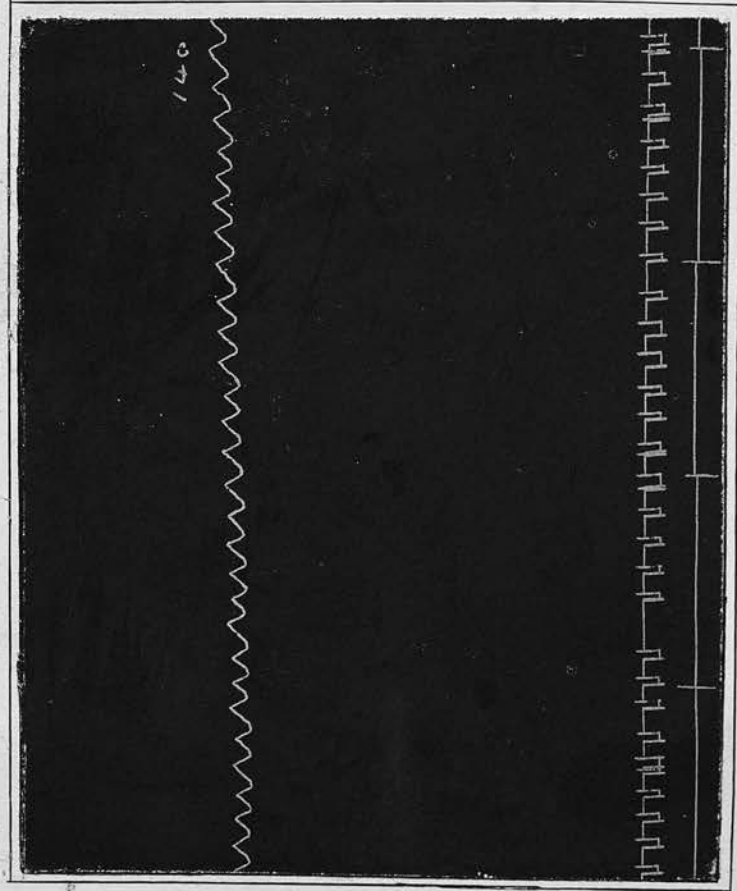
Cat, female
wt 1500 gms.
9/2/21

110 mm Manometer



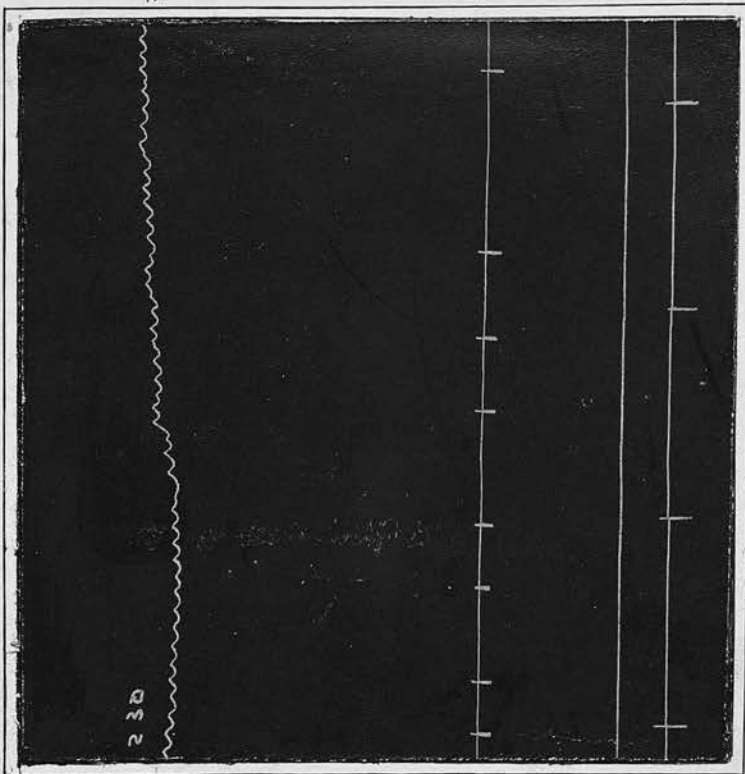
Signal = free flow from outlet.
Time in minutes

Spontaneous Waves in Pulmonary Circulation.



140 mm.

Signal down
= free flow
from outlet.



230

230 mm

titer.

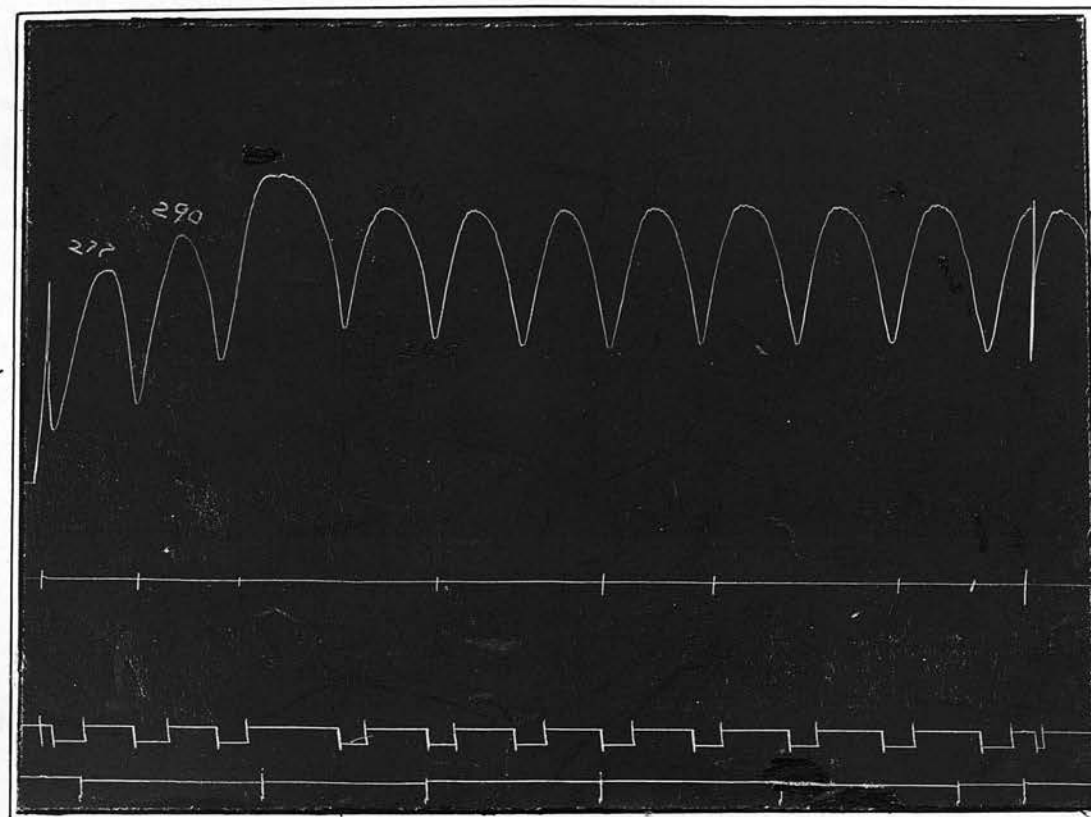
Fig. 328

The manometer is attached to an Ellis piston recorder by which the changes in pressure are shown graphically in a kymograph in the usual way.

The accompanying tracings give examples of records obtained in this way. Practically all the tracings were obtained during perfusion with Ringer-Locke fluid made up without bicarbonate although a few waves have been observed occasionally at the beginning of perfusion experiments with ordinary Ringer-Locke fluid. The temperature of the perfusion fluid was $37^{\circ} - 39^{\circ} \text{ C.}$, and it was noted that the waves were most frequently obtained in young and robust animals whose tissues were moist and well nourished.

The waves it is seen may be regular (Fig. 30) or irregular (Fig. 30). They may be slow at first as seen in Fig. 31 and become more rapid or vice versa as seen in figures ^{30 & 32} where the slowing is apparently the result of oedema which was noted to have supervened. The rate varies from one to ten per minute. In the same animal waves have been obtained at pressures varying from 110 mm. to 230 mm. of perfusion fluid. ^{Fig 32B.} In one instance the contraction was so great as to completely occlude the pulmonary circulation as seen by a temporary cessation of flow from outlet tube from the left auricle. (Fig 30, 32) It/

A

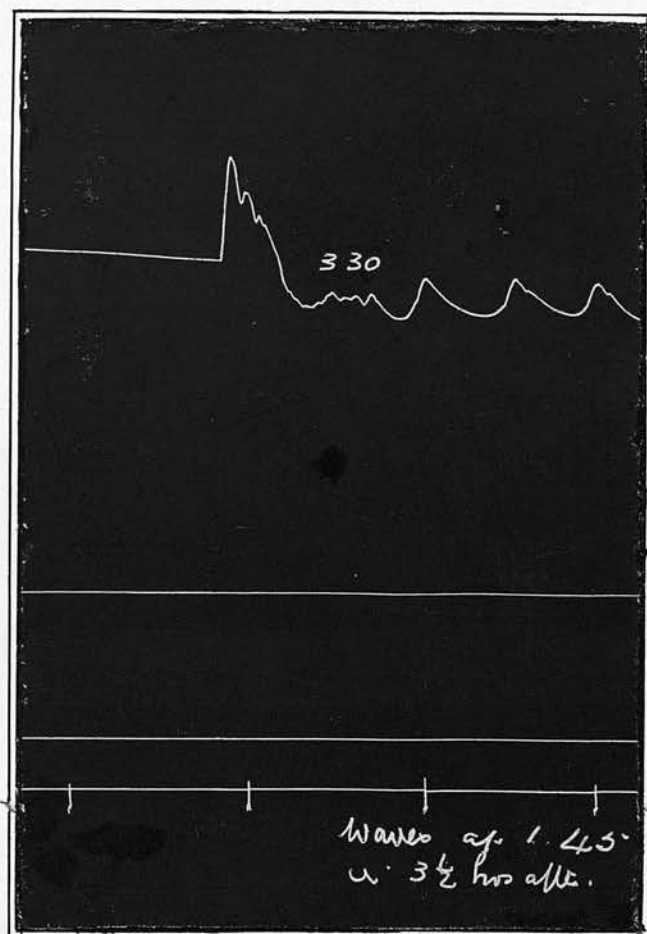


Pressure of
entering perfusion
fluid.

Tiller - (irregular)

Signal - down = free
flow from outlet -
Time.

B



A - Waves during rapid
increase of pressure

B Waves 3 1/2 hours after
commencement of experiment
and stimulation by air-blast

Cat, female (young)

wt. 1650 gms.

4-2-21

Waves at 1.45
u. 3 1/2 hrs after.

Cat, male.
wt- 2900gms.
1/12/20.

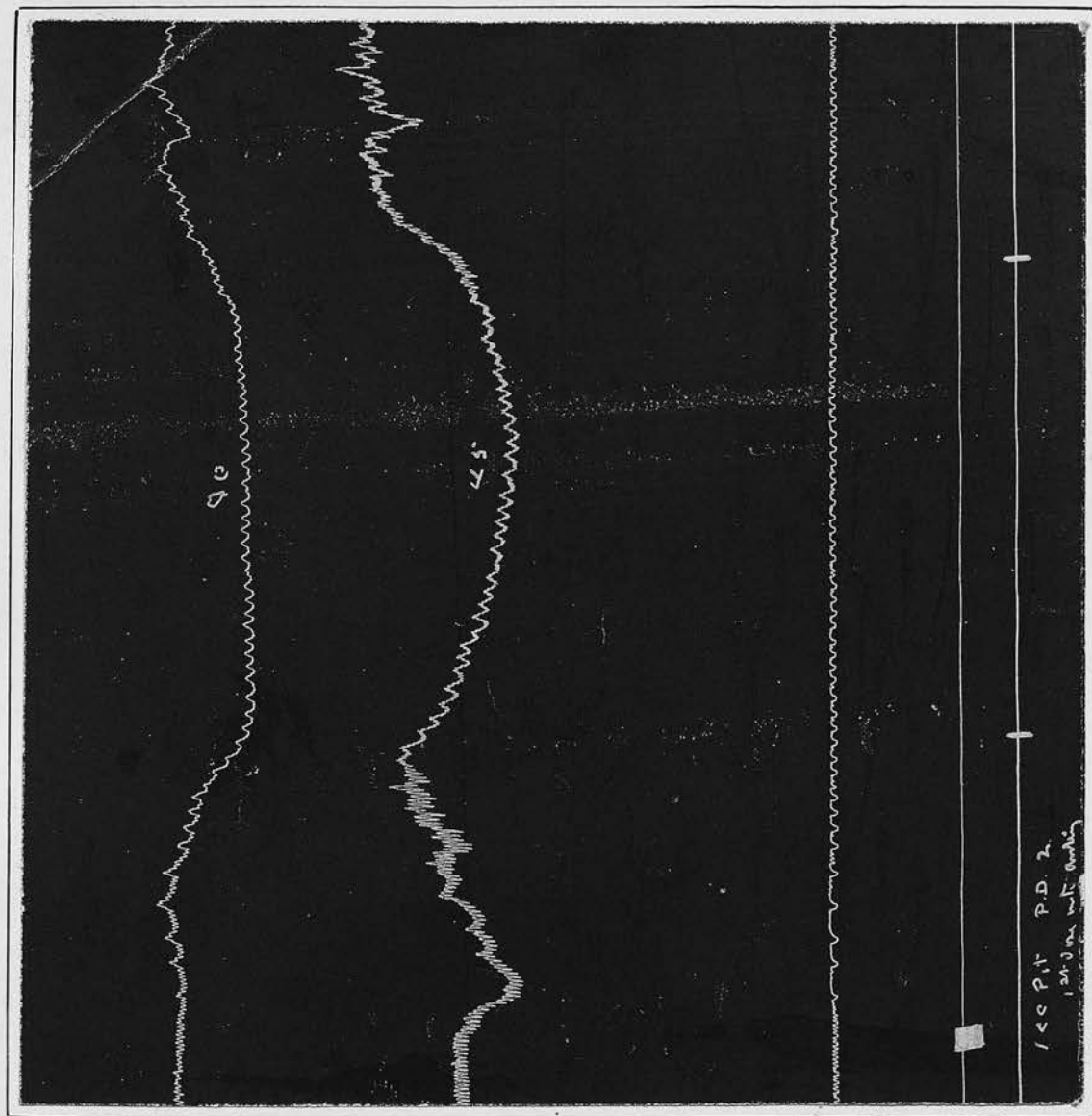
Tonic waves in arteries during perfusion of

systemic circulation in Ringo Locke Sol. at 37°C & 250 mm Hg Press.

Note There was ^{almost} complete occlusion of the circulation as
shown by cessation of flow to the fillo.

Method - Inlet cannula - aorta
Outlet - " - rt. auricle.

Fig. 44



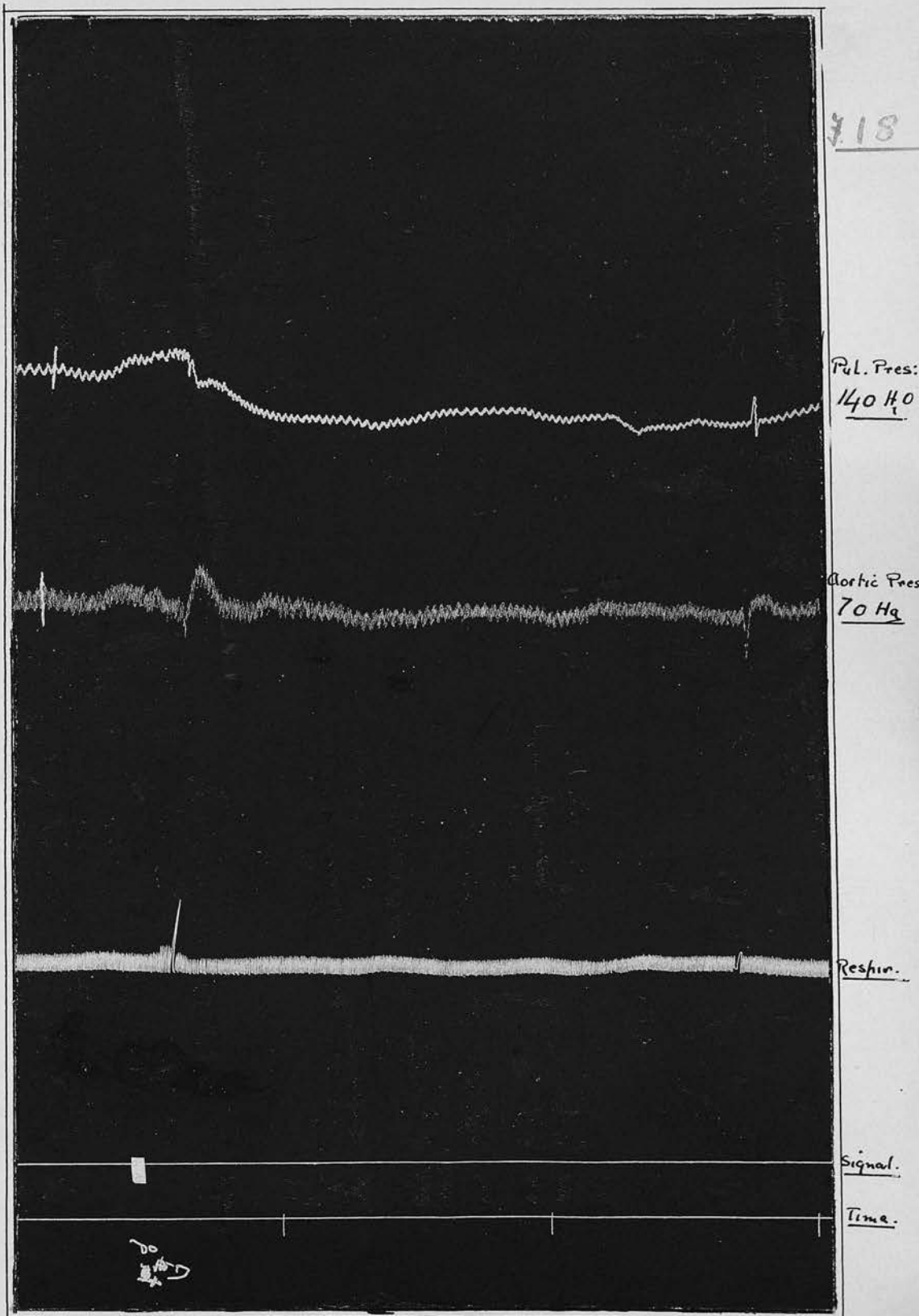
Cat, female
wt. - 2900 gms.
chl. - .4 gm.
19:10.20.

1cc Pit. (P.D.) 1st Dose into artery.

Fall in pulmonary due to cardiac variation

Note the parallelism of the falls in both, also at the end of tracing. Some irregularity of breathing.

718



at female (pneum)
Wt 2500
CL Hy 45 gr

↑
Simultaneous points.

ICC Pit. Ext. $2\frac{1}{4}$ H₂O Dose. into vein

Note Pulmonary rise and fall similar to results got in perfusion. Cannot be accounted by change in aortic pressure which has not changed much. The 27th 30th doses gave no marked change

It is seen that the fluid began to flow freely from the outlet tube just at the end of relaxation and continued during the early part of contraction.

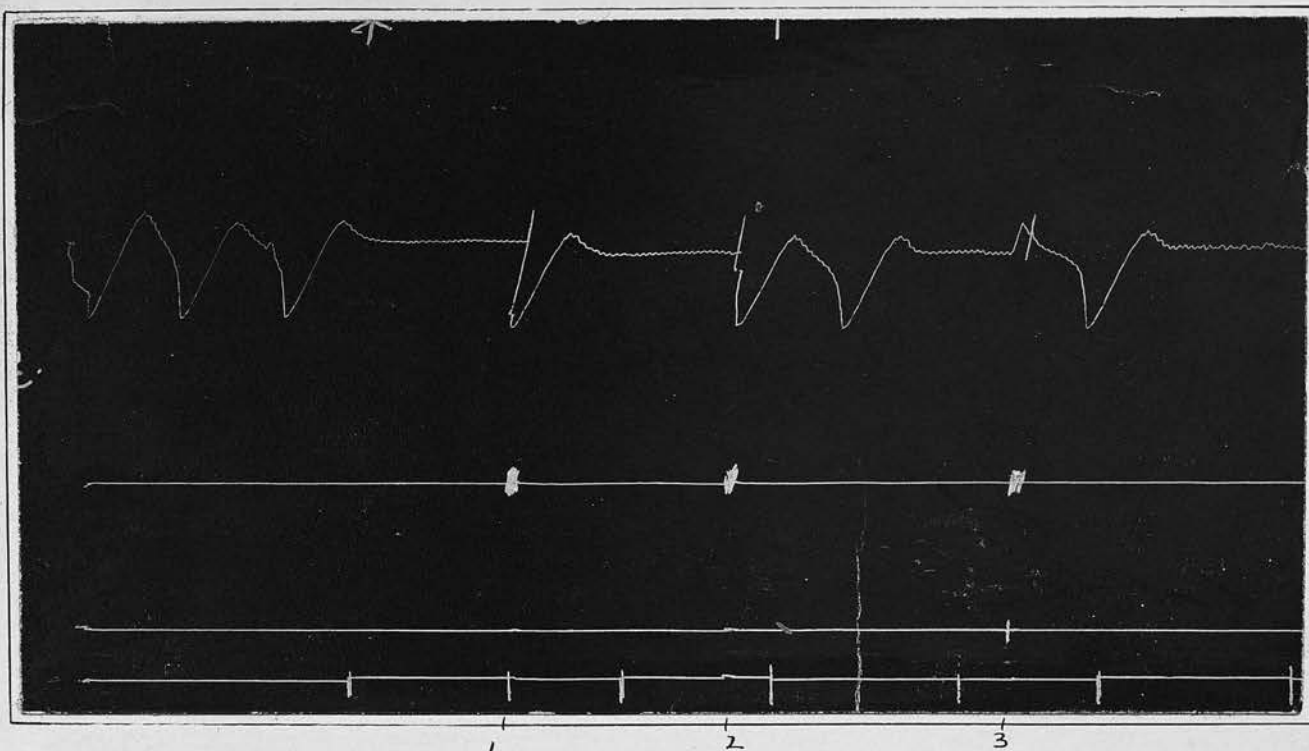
Such rhythmic contractions and relaxations continued for two or three hours if care was taken to avoid undue distension of the arteries (Fig. 33B)

Figure 30A indicates the existence of longer waves.

The contractions are seen to become gradually slower and eventually stop for a short period after which a small contraction occurs and the more rapid contractions and relaxations recommenced. These longer waves may be taken to be tonic waves of contraction similar to those which have been described by Roucato in rings of arteries as interfering with the rhythmic waves. As the experiment progressed these tonic waves became more pronounced and gradually passed into rigor with complete occlusion of the pulmonary circuit. In the early stages however the tonic contraction was overcome by increasing the pressure of the perfusion fluid and stimulation

(Fig. 32). Stimulation was effected by subjecting the lung alveoli to an air blast for a few seconds. This is shown in figure 34 and figure 35 which are tracings from different animals in which the waves subsequently continued for several hours.

Instances/



Cat, female.

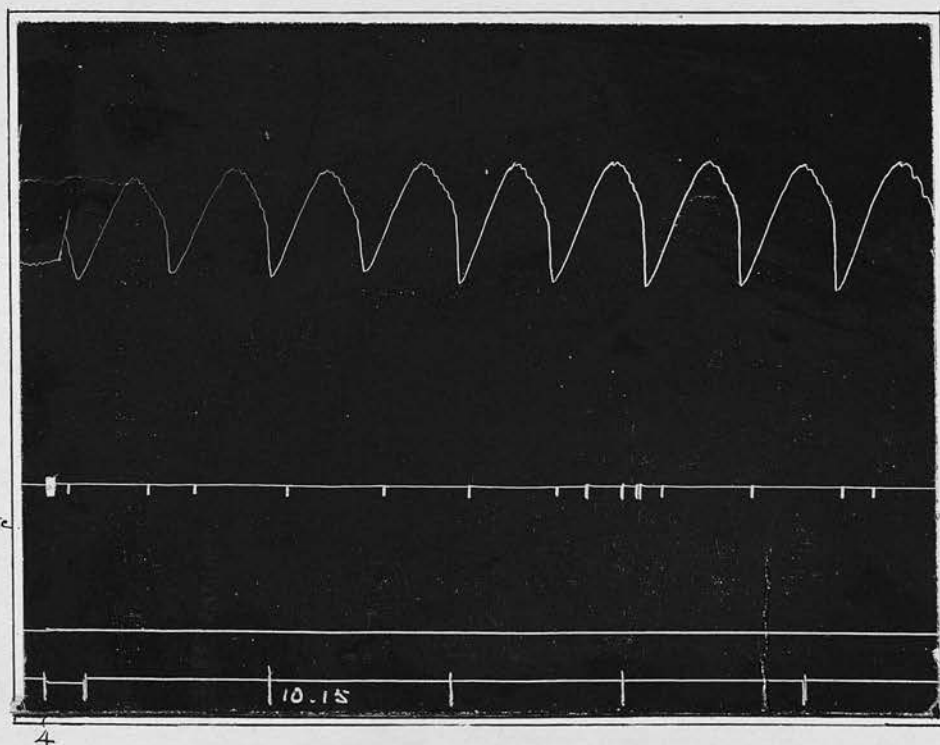
Wt. 1600 gms.

Perfusion with

R.L. Solution

Without Bicarbonate

4:2:21



NB

Beginning of

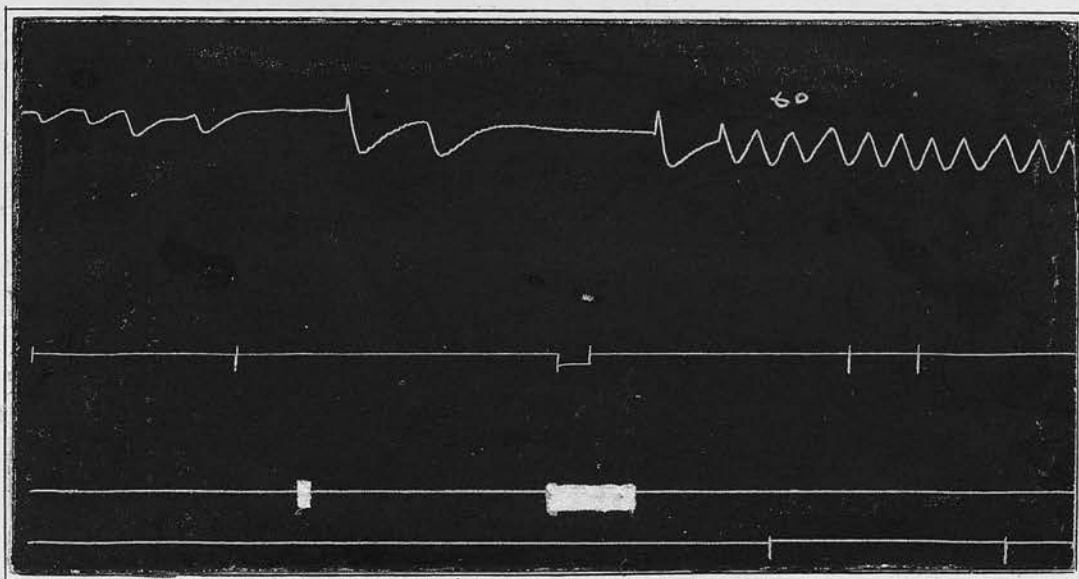
experiment. Lever
not writing perfectly
- cyclically.

Tiller not working
properly.

Stimulation by Distension of Lung.

Note 1, 2, 3 - less successful

4 - long series of waves produced



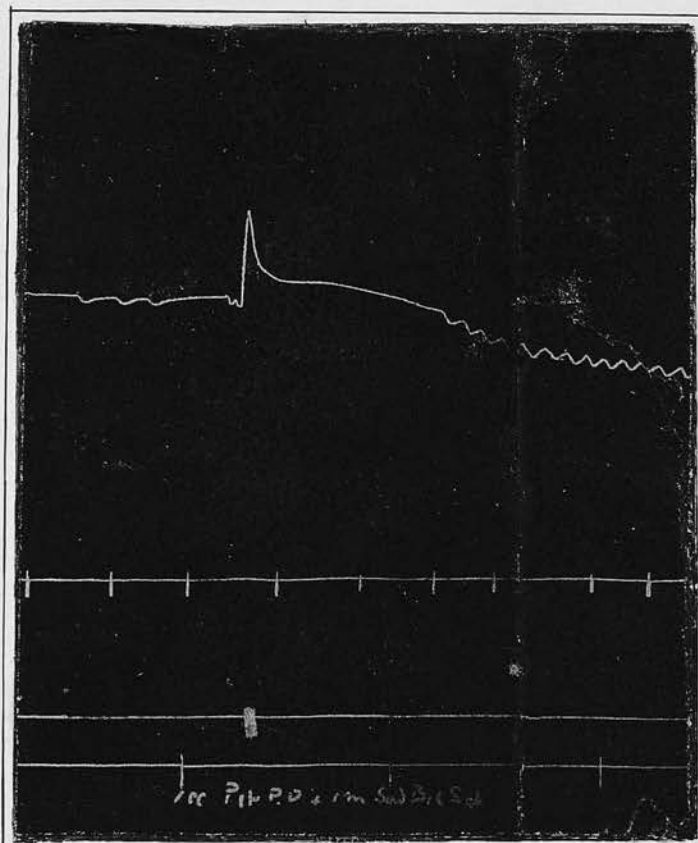
Pressure of
entering perfusion
fluid

Tiller (irregular)

Signal

Time

A



Pressure of entering fluid

Tiller

Signal

Time

B

Cat, female
wt. 1500 gms.
9/2/21

Methods of stimulating the production of spontaneous waves.

A - Distension of lungs by blast of air.

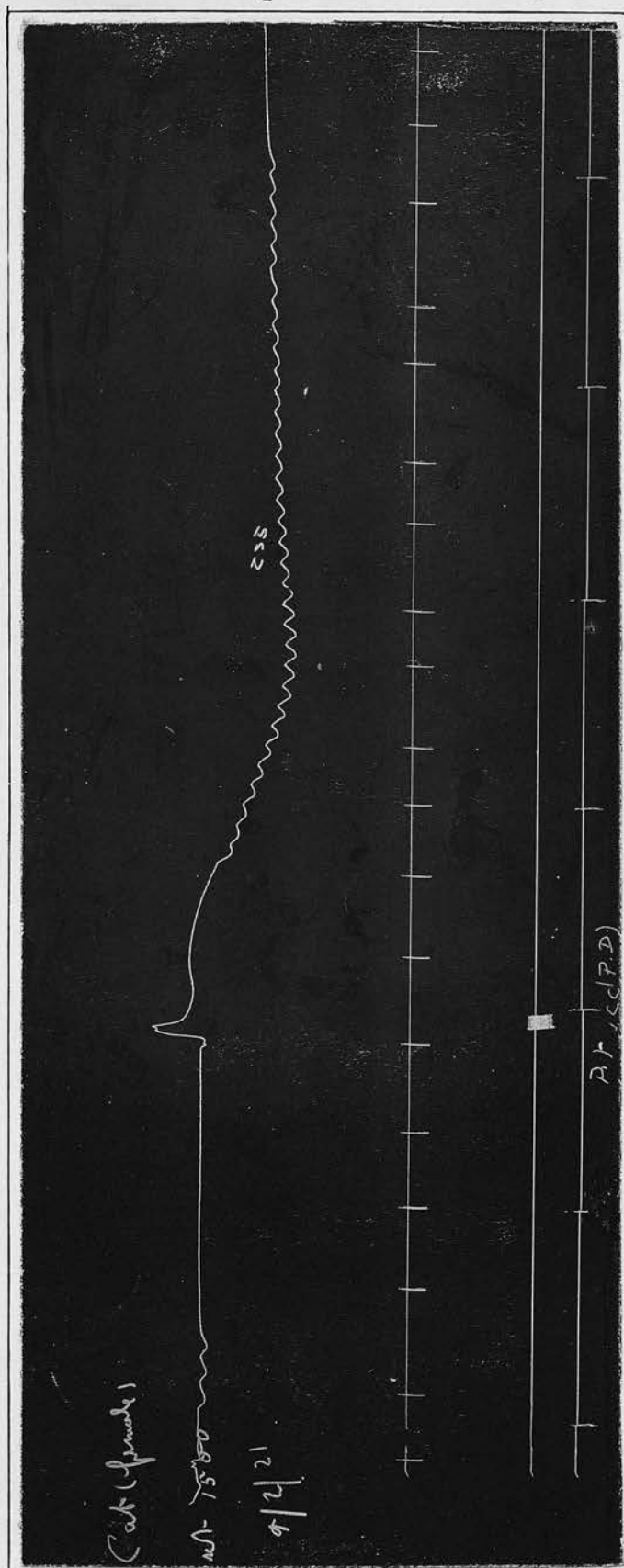
Note, 1st stimulation only followed by two waves

B - Stimulation by Pituitrin.

Both perfusion in R.L. Sm. without bicarbonate.

Instances are shown in which the first blast was of no value or was followed by one or two contractions, while subsequent similar stimulation resulted in a series of contractions and relaxations lasting some time. Pituitary extract had also a marked stimulating effect on previously quiescent vessels. This is well shown in figures 36 and 12 which also show waves at different pressures. Sharpey Schafer and Lim have noted the occasional occurrence of waves after adrenalin, and a similar action of pituitary extract on rings of arteries was observed by De Bouis and Suzanna. Cow also found the same stimulative action of adrenalin in relation to isolated arterial rings. In his paper he asks himself ^{are} ~~is~~ these waves which he found at the rate of one in twenty-five seconds Traube-Hering waves which are usually one in thirty seconds. Unfortunately he leaves the subject there.

It may be added that pituitrin (P.D) plus sodium bicarbonate had a more stimulating effect than pituitrin alone, which occasionally inhibited the waves. Sodium bicarbonate alone caused temporary inhibition as seen in figure 37 . The fact that in the case of pituitrin the production of waves ^{during} occurs _A relaxation is interesting as it is the converse of adrenalin which causes the stimulation of/

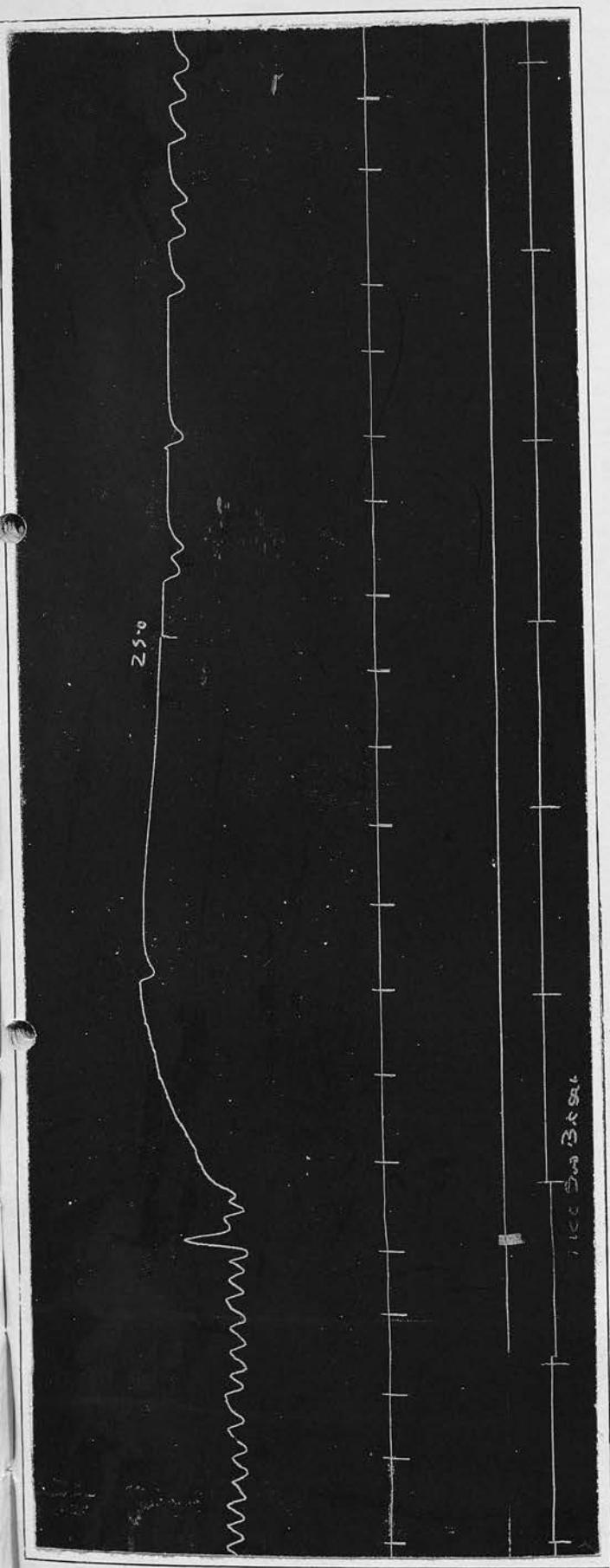


Stimulation of waves by Pituitrin. 1cc (P.D.) 5th Dose

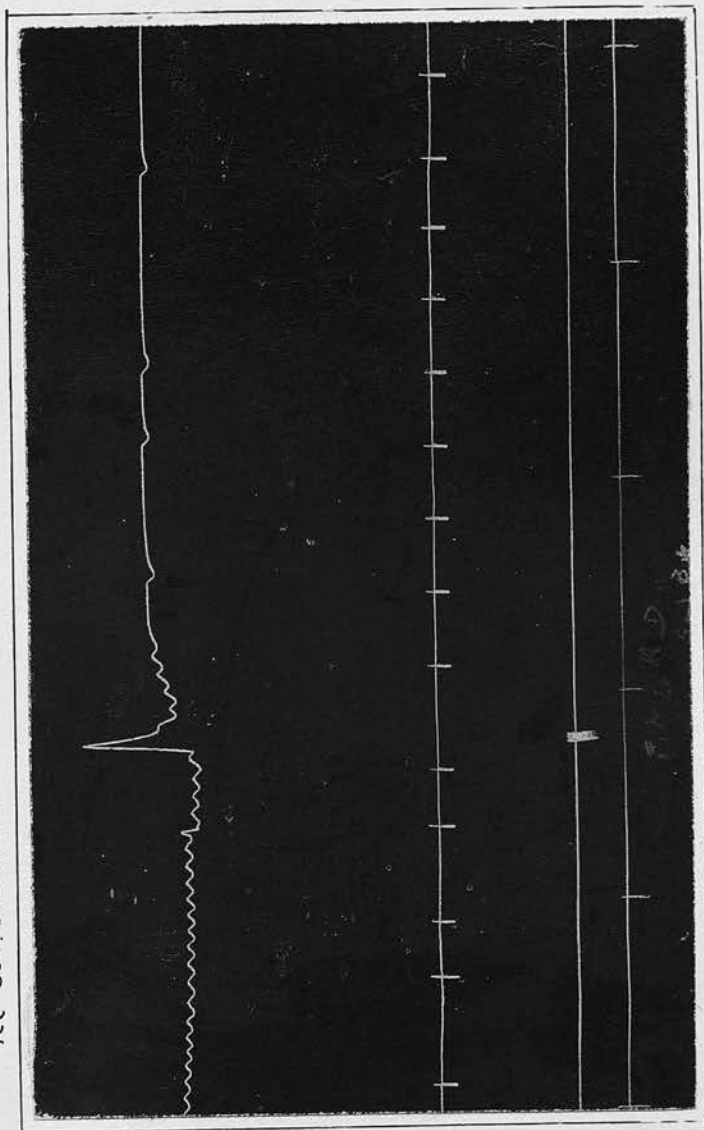
During perfusion.

Cat, female.
Wt. 1500 gms.
9-2-21

Perfusion in R.L. fluid without bicarbonate



ICE Sod Bic Sol.



Note: Pituitary Extract or Sodium Bicarbonate Separately may inhibit waves (cf Figs 7 B)

Cat, female
wt - 1500gms.
9.2.21.
Perfusion in R.L. Sol. without bicarbonate

of waves during contraction and it would go to prove that whatever the actual factor in the pituitrin which causes the dilatation, the stimulative property of the autocoid on plain muscle is not thrown out of action. Further reference will be made to this in the addendum on the action of pituitrin.

The possibility of these waves being due to any cause other than contraction of the lung vessels has been carefully considered. At first sight it might be thought that the waves are the result of the artificial respiration which might cause compression of the lung capillaries. The rate however is quite different and indeed small respiratory waves are also seen in many of the tracings.

The occurrence of the waves at different pressures, the variance of rate in the same animal, the persistence of the waves for prolonged periods, their stimulation by distension of the lung alveoli, by pituitrin and by adrenalin which are well known activators of plain muscle are all in favour of the contention that the waves are due to constriction of vessels. This is supported by the finding of similar waves in isolated arterial rings by other investigators.

Slow tonic waves^{*} have been found (Fig. 44) during perfusion of the systemic circulation while more/

**. Also by Roncati in arterial rings.*

more rapid waves - 40 per minute - were found during perfusion of the hind limbs of a cat but they were too small to be recorded. Rhythmical contractions of isolated arterial rings have also been recorded by previous observers. The actual demonstration of these waves in perfused arteries may be considered but a question of time and is outwith the scope of the present research.

The knowledge of such spontaneous waves in blood-vessels throws considerable light on the variations so frequently obtained in blood-pressure tracings. These may be considered to be of few varieties; those due to variation in the heart action as evidenced by simultaneous rise or fall in the systemic and pulmonary pressures; those due to respiration characterised by opposite effects in the systemic and pulmonary pressures; those due to vaso-motor centre probably but not necessarily seen in both systems and slow in character; and those due to the arteries themselves in rhythmical contraction. Figure 39 shows variation probably due to heart, ~~the others~~ Those due to respiration ~~which~~ are ~~also~~ readily seen in early stages of asphyxia. In Figs. 40 and 41 are seen waves presumably due to the vessels themselves as in one instance they occur/

occur in the systemic without affecting the pulmonary and the other an obvious result of the action of pituitrin which has stimulated the plain muscle in the same way as was seen in the perfusion experiments.

The following concluding remarks are perhaps not strictly relevant in connection with the pulmonary circulation, but as they contain a new aspect - or rather a revival of old conceptions based on more modern knowledge they have been considered worthy of inclusion.

At an early date Poiseuille suggested that such rhythmic movement indicated a propulsive force and it may be so in some of the invertebrates in which the heart is but little differentiated. It seems however more justifiable to consider such rhythmic action as a remnant of the lower and simpler vascular systems which in the higher animals has been adapted for use in connection with the heart.

It/

It has been shown that the arteries have an inherent rhythm of their own and also that arteries respond by contraction to a dilating force. One cannot avoid noting the analogy that the ventricles of the heart have a rhythm of their own yet beat more rapidly as a result of stimulation from the sino-auricular node - in mammals by way of the auriculo-ventricular bundle. If the conducting fibres be severed, e.g. by a ligature - in the frog at the sino-auricular junction - the ventricle may after a period of stoppage resume contraction and almost certainly if a second ligature be tied at the auriculo-ventricular junction. This latter fact has been generally considered due to a distension of the ventricle or a stretching of its fibres.

It would not therefore be considered an impossible hypothesis to suggest that something similar occurs in relation to the arteries, in some animals at least, namely that the smooth muscle of arteries contracts normally in response to the pulse wave. It may be that this is just sufficient to counteract the distending influence of the pulse wave and assists in storing up the heart's energy - a process hitherto ascribed purely to the elastic tissue of the vessel walls, and it may be noted that in this very/

very connection Lister remarked upon the very slight apparent change of calibre of human arteries in comparison to the pulse wave and suggested the influence of the muscular tissue apart from its mere elasticity. If such a hypothesis be allowed it is easy to go a step further and suggest in asphyxia^l or anaemic conditions of the bulbar centres the regulating action of the vasomotor centre becomes upset, the synchronism between the heart and arteries becomes abolished and waves (Taube Hering) appear in tracings of the blood pressure similar to those which are found in the perfusion experiments described above.

If such autochtonicity is present it is justifiable to assume that the activity may be tonic as well as rhythmic, indeed the existence of tonic as well as rhythmic waves has been indicated above.

Such activity would therefore account for the recovery of vascular tone which it is well known succeeds its loss after cutting of the spinal cord; a fact hitherto attributed to subsidiary vasomotor centres in the spinal cord.

The fuller knowledge of the physiology of the blood-vessels and their associated ganglia will in the process of time gradually solve the many interesting problems which beset alike the scientist and clinician.

In/

In conclusion I have to thank Sir E. Sharpey Schafer for the excellent opportunities for research he has afforded me and for the valuable advice he has given throughout.

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Simultaneous waves due to cardiac variation.

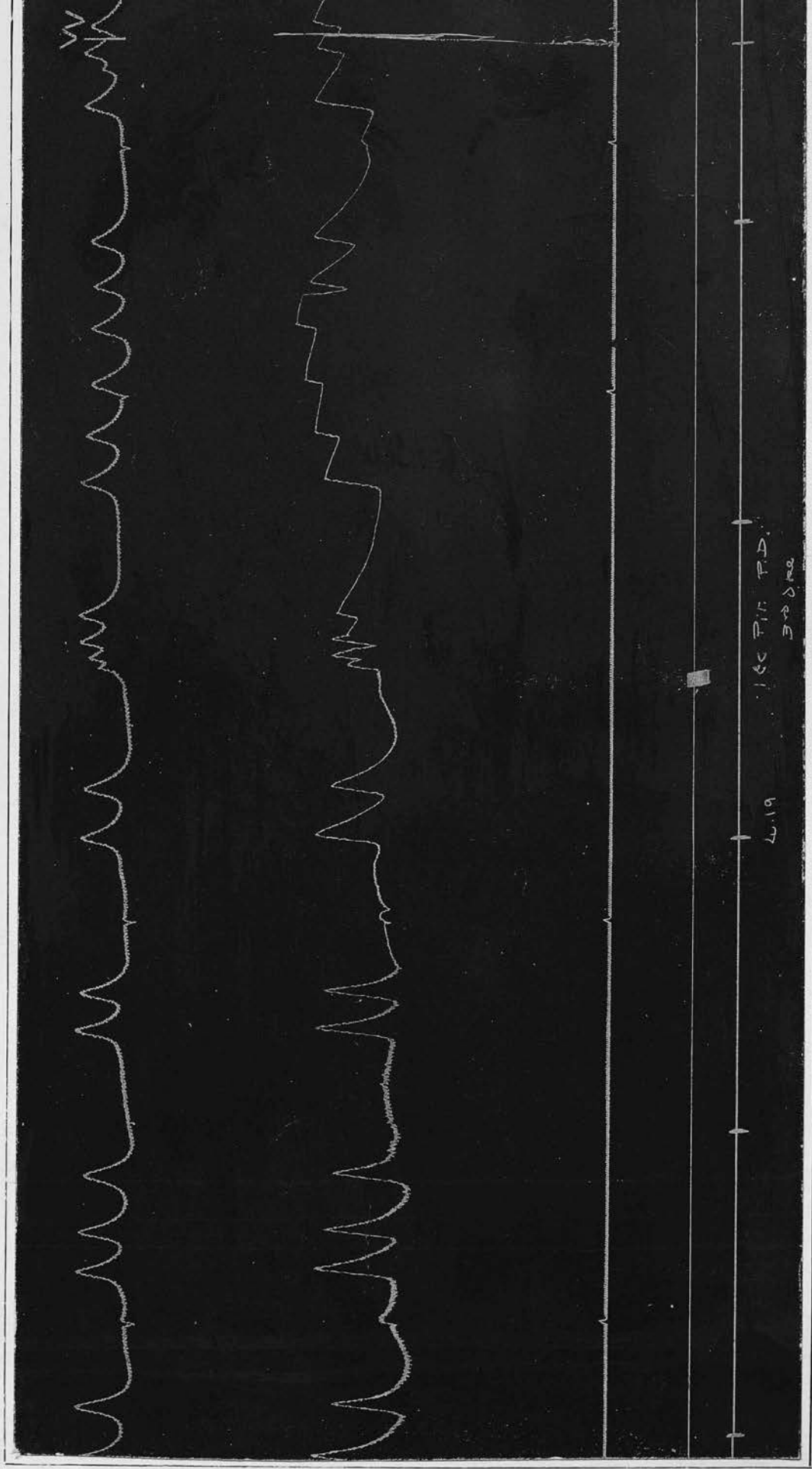
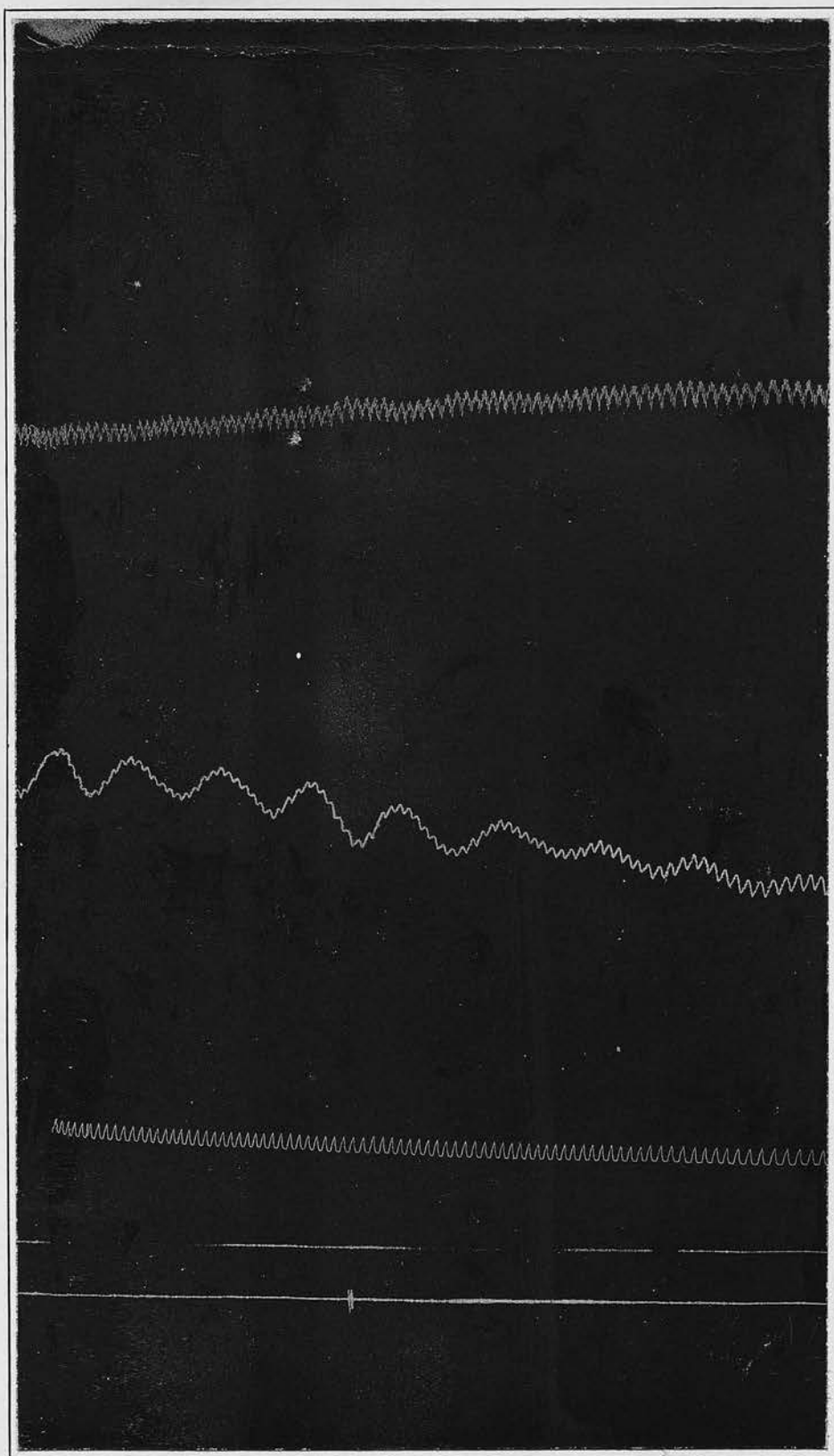


Fig. 40.



Pulmonary blood-
-pressure

Systemic blood-
-pressure

Respiration

Time

Taken at the
beginning of an
experiment

Waves in Systemic Circulation. only (in living animal.)

Shows the independence of the two circulations.

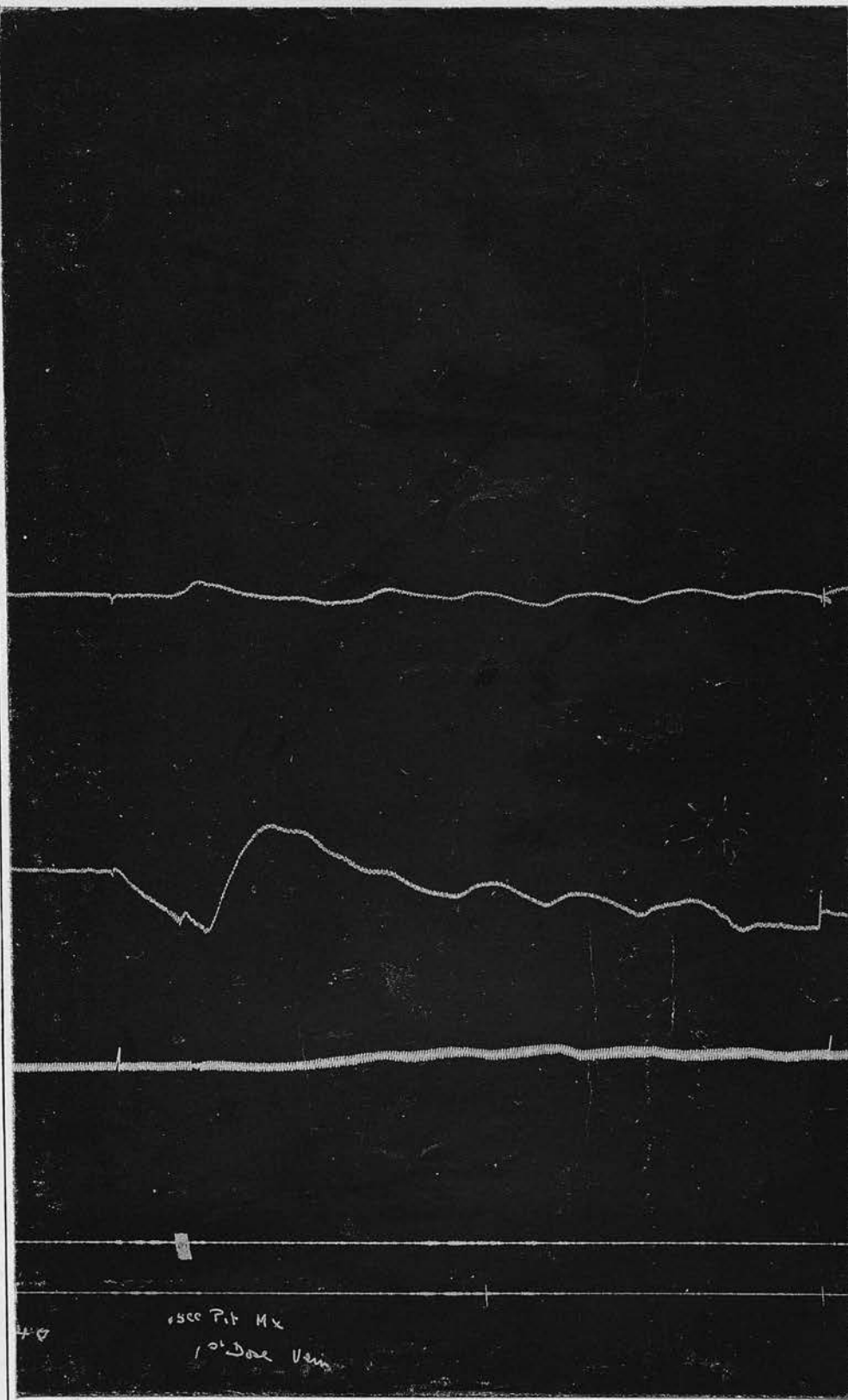
A central action would be expected to affect the pulmonary also.
These waves are probably due to peripheral changes.

Rabbit, male.

Wt. 2500 gms

Chloral .5 gm.

Fig. 41.



Pulmonary blood-
-pressure 110 mm Hg.

← Systemic blood-
-pressure 80 mm Hg.

Respirations

Signal

Time in minutes.

rabbit, male

Wt 2290 gms

Chloral .5 gm.

Pituitrin .5 cc. (Martindale)

.5 cc Pit Mx

1st Dose Venn

.5 cc Pit. (Mart)

1st Dose into vein

Production of Waves by Pituitrin.

in Living Animal.